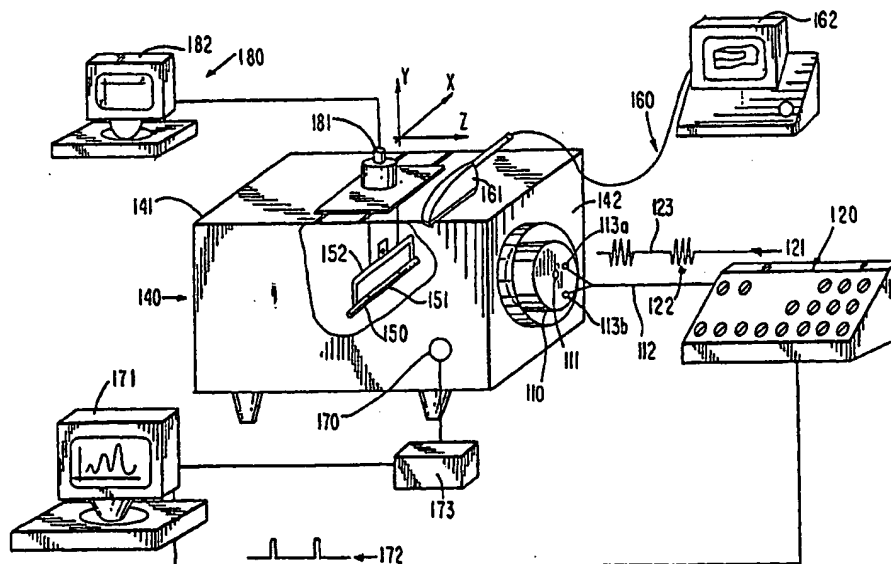




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(54) Title: DUAL TRANSDUCER ULTRASOUND LYSIS METHOD AND APPARATUS



(57) Abstract

An apparatus and method for the application of ultrasound to a location within the body is provided. A cavitation detection system is included so that the effectiveness, and safety of the ultrasound can be monitored during ultrasound treatment. A non-invasive ultrasound system (100) includes a therapeutic focused ultrasound transducer (110).

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DUAL TRANSDUCER ULTRASOUND LYSIS METHOD AND APPARATUS

CROSS REFERENCE TO RELATED APPLICATIONS

5 This is a continuation-in-part of Ser. No. 08/939,289, filed September 29, 1997, the contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

10 The invention relates generally to medical devices and more particularly to a method and apparatus for delivering ultrasound energy to a treatment location within a human or other mammal.

The use of ultrasound devices for ablating, lysing or removing material obstructing blood vessels in humans and to otherwise apply ultrasound to locations within the body for therapeutic purposes has been proposed in the art. One such
15 device for removing material obstructing blood vessels is in the form of an elongated ultrasound transmitting probe. This device includes a cavitation generating tip at the distal end of an elongated transmission member. A transducer is used to convert an electrical signal into longitudinal mechanical vibration, which is transmitted to the tip by the transmission member and causes cavitation within the blood vessel to ablate or
20 lyse the obstruction.

One drawback to such a device is the need to insert and advance the device through a blood vessel to the treatment location. This raises various concerns, such as the opportunity for breakage of apparatus parts within the body, injury to the body from the probe itself and so forth. Another drawback is the need to pump
25 cooling fluid down the length of the device. Examples of such devices are discussed in the following patents, applications and publications, the contents of which are incorporated herein by reference: 5,163,421, issued November 17, 1992; 5,269,297, issued December 14, 1993; 5,324,255; 4,474,180; Ser. No. 08/858,247, filed May 19, 1997 and Julian Frederick, "Ultrasonic Engineering", John Wiley and Sons (1965).
30 However, it is desirable to provide an improved system and method which overcome drawbacks of these conventional devices and methods.

The non-invasive use of ultrasound has also been proposed. For example, U.S. Patent No. 5,524,620 dated June 11, 1996, the contents of which are incorporated herein by reference, describes a non-invasive apparatus and method in which focused acoustic energy is used to ablate a thrombus without the need for invasive devices or drugs. However, non-invasive ultrasound systems can exhibit insufficiently satisfactory results. For example, high power is generally needed to cause adequate lysis. This high power is potentially dangerous and thus, it is desirable to operate a non-invasive system more efficiently, at lower average power, in order to provide a greater margin of safety. The effects of non-invasive ultrasound devices on various locations within the body can also be difficult to predict and control.

Accordingly, it is desirable to provide an improved system and method for the non-invasive application of ultrasound which overcomes inadequacies of the prior art.

SUMMARY OF THE INVENTION

Generally speaking, in accordance with the invention, an apparatus and method for the application of ultrasound to a location within the body is provided. The apparatus can advantageously operate at a pulse duration below about 100 milliseconds and in the range 0.1 milliseconds to 100 milliseconds and a pulse repetition period below about 1 second and in the range of 1 millisecond to 1 second. Duty cycle ratios over 5 and preferably over 8 are also advantageous. Therapeutic applications of ultrasound such as for assisting in the treatment of medical conditions such as cancer and/or other ailments are also provided. Treatment can be controlled by monitoring the size and location of the cavitation bubble cloud with an ultrasound imaging device and adjusting parameters such as power or pulse length manually and/or automatically to change the size of the cavitation bubble cloud as desired. Treatment can also be controlled by monitoring the sound given off during cavitation.

Accordingly, it is an object of the invention to provide an improved apparatus and method for treating locations within the body with ultrasound.

A further object of the invention is to provide a method and apparatus for determining ultrasound application parameters.

Yet another object of the invention is to provide an apparatus and method for therapeutic applications of ultrasound.

5 Still other objects and advantages of the invention will in part be obvious and will in part be apparent from the specification and drawings.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others, and the apparatus embodying features of construction, combinations of elements and arrangements of
10 parts which are adapted to effect such steps, all as exemplified in the following detailed disclosure, and the scope of the invention will be indicated in the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the invention, reference is had to the following description taken in connection with the accompanying drawings, in which:

15 FIG. 1A is a schematic perspective view of a system for the non-invasive use and testing of ultrasound energy;

FIG. 1B and 1C are front and side views of the transducer shown in FIG 1A;

20 FIG. 2 is a graph showing hydrophone output, in decibels, as a function of transversal displacement of the hydrophone along the Y axis to establish the focal width of ultrasound in the Y direction;

FIG. 3 is a graph showing hydrophone output voltage as a function of transducer input voltage, showing that electric potential above 160 volts, and therefore increased wattage, caused a decrease in hydrophone output as a result of exceeding the
25 cavitation threshold of the medium;

FIG. 4 is a graph showing hydrophone output voltage as a function of displacement of the transducer along the Z-axis for both short duration pulses and relatively longer duration pulses, showing that a longer pulse duration (τ) can initiate cavitation;

FIG. 5 is a graph showing hydrophone output voltage as a function of Z-axis displacement for various pulse durations, showing that longer pulse durations were associated with larger decreases in acoustic amplitude after exceeding the cavitation threshold;

5 FIG. 6 is a graph showing hydrophone output voltage as a function of Z-axis displacement for transducer inputs of varying voltage, showing that cavitation was evidenced by a decrease in actual hydrophone output from the theoretical output;

FIG. 7 is a graph showing change in percentage of clot mass dissolution as a function of change in the pulse repetition period (T), showing that an appropriate
10 pulse repetition period has a significant effect on the efficiency of clot lysis;

FIG. 8 is a graph showing percentage of clot mass dissolution as a function of pulse duration (τ), showing a strong dependency of clot dissolution and danger to the blood vessel on pulse duration;

FIG. 9 is a graph showing rate of clot mass dissolution as a function of
15 intensity at the focal area;

FIGS. 10A and 10B are ultrasound images of a clot within an artery segment, before and after ultrasound treatment;

FIGS. 11 and 12 are graphs showing microphone output voltage as a function of ultrasound peak intensity in a buffer solution and in a clot, showing that
20 ultrasound initiated randomly, but that once initiated, it could be maintained at decreased intensities and that the threshold and slope are different for the buffer and clot;

FIGS. 13 and 14 are graphs showing microphone output as a function of ultrasound intensity, when blood is acted upon by ultrasound of different pulse
25 repetition periods (T), showing that shorter T's correlate to lower intensity thresholds and ultimately lower cavitation intensity;

FIGS. 15 and 16 are graphs showing the influence of pulse duration on cavitation activity of a buffer solution and blood, respectively;

FIG. 17 is a graph showing microphone output, which is related to cavitation activity, as a function of pulse duration in both a blood and a buffer solution;

FIG. 18 is a graph showing percentage of weight loss of a clot as a function of ultrasound intensity for a non-degassed and degassed sample, showing a lower intensity threshold and lower intensity requirement for the non-degassed system;

FIGS. 19A and 19B are two graphs showing percentage of clot dissolution as a function of pulse duration at two different power settings, at $T = 7$ ms, showing increased clot dissolution with increased intensity and that optimal pulse durations exist for certain other parameters;

FIGS. 20A, 20B and 20C are three graphs showing percentage of clot dissolution as a function of pulse duration (τ), pulse repetition period (T), and pulse duration (τ), respectively, at intensities of 1400 W/cm^2 , 1400 W/cm^2 and 1300 W/cm^2 respectively and shows that optimal parameters can be intensity independent;

FIG. 21 is a graph showing percentage of clot dissolution as a function of ultrasound intensity, manifesting threshold for clot lysis;

FIG. 22 is a graph showing the weight of unlysed clot as a function of ultrasound intensity, manifesting a threshold for clot lysis;

FIG. 23 is a perspective view of an invasive type ultrasound transmission system, constructed in accordance with an embodiment of the invention;

FIGS. 24-27 are graphs showing cavitation activity as a function of transducer power, showing the difference between continuous and pulsed activation;

FIGS. 28-30 show ultrasound probe temperature in activated and unactivated states, both with and without the use of cooling fluid, in a continuous wave mode of probe operation, and in duty cycles of 8;

FIG. 31 shows a non-invasive ultrasound treatment system with a combined ultrasound imaging and ultrasound treatment transducer and a display screen permitting an operator to monitor the treatment; and

FIGS. 32A, 32B and 32C show that adjusting pulse duration can affect the size of the cavitation bubble cloud within a vessel.

DESCRIPTION OF PREFERRED EMBODIMENTS

Significant therapeutic effects can be achieved by applying ultrasound to locations within a living body. Generally, a transducer converts an electrical signal to mechanical vibration, which causes the propagation of ultrasound waves through some medium or media. If these waves are of sufficient intensity, they create cavitation within a medium at a desired location as micro bubbles are formed and collapse. This generates extraordinarily high activity at the cavitation site.

A transducer can be operated in a continuous mode or in a pulsed mode. In a continuous mode, the signal to the transducer is always causing the transducer to generate sufficient vibration to maintain cavitation at the desired location. In a "pulse" mode, the signal amplitude is reduced sufficiently (or eliminated) to permit cavitation to pause between pulses of high amplitude during which cavitation occurs. Certain conventional pulsing methods apply ultrasound in one to several second doses, followed by pauses of approximately equal duration or even durations longer than the duration of the activating signal. This is conventionally performed to permit objects which became hot during the activation process to cool down. It has been discovered that applying ultrasound in an improved pulsed mode can provide substantial advantages, compared to conventional pulsing modes of operation.

Referring to FIG. 1A, an example of a system for providing the non-invasive application of ultrasound to a test sample in a model representing a body part, which can be readily modified to apply ultrasound to a location within a living body, is shown generally as non-invasive ultrasound application system 100. Non-invasive ultrasound system 100 includes a therapeutic focused ultrasound transducer 110, which is activated by an electrical signal from a signal generator 120. Therapeutic transducer 110 can be constructed to operate at up to 750 KHz and can be formed with a 1-3 ceramic composite. A 1-3 composite transducer includes rods of PZT inserted into a polymer support and has very high energy transfer efficiency. Front and side views of one embodiment of transducer 110 are shown in FIGS. 1B and 1C. Therapeutic transducer 110 includes a hole 111 at the center thereof. Hole 111

permits the use of an optional ultrasound imaging probe (not shown) which can guide and monitor the therapy with ultrasound during application. One example of a suitable transducer, which was used in experiments presented herein, is about 45 mm thick, has an overall radius of 46 mm, a central active area with a radius of 40 mm and a central bore with a radius of about 10 mm. Electrical connections are on either side of the central bore at disk shaped depressions having an 8 mm radius. Alternative transducers can be substituted.

To operate transducer 110, generator 120 sends a signal 121 through a pair of electric wires 112, which are coupled to transducer 110 at attachment points 113a and 113b. Signal 121 is formed with a plurality of energy pulses 122 of duration τ at an amplitude (A) and a frequency (f). As used herein, a pulse will be considered the "on" portion 122 of signal 121, which is of sufficient amplitude to maintain cavitation and is followed by an "off" section 123 of signal 121 of insufficient amplitude to maintain cavitation. The duration of time between the beginning of successive pulses 122 is referred to as pulse repetition period T. It has been determined that pulse duration τ is advantageously significantly smaller than pulse repetition period T.

To model the effects ultrasound emitted from therapeutic transducer 110 would have on a location within a living body, a model system 140 was constructed. Model system 140 includes an open Plexiglas water tank 141 with a hole in a front side 142 for inserting therapeutic transducer 110. Tank 141 was filled with water, which was either degassed or non-degassed, depending on the particular experiment to be run. When water was not degassed, it included small air bubbles which served as a nuclei for cavitation initiation. Decreasing the number of bubbles in the water increases the energy needed to initiate cavitation.

To obtain information about the focal region of ultrasound emitted from transducer 110, a hydrophone (not shown) was positioned at various locations within a dedicated tank. It was found that when activated by generator 120 at low intensities below the cavitation threshold, transducer 110 creates an acoustic field with a focal region having an elongated ellipsoid or cigar shape.

To obtain information regarding the effects of ultrasound on clots within a living body, a bovine vessel 150 having a clot 151 therein or a clot attached to the front of a bovine vessel wall was suspended within tank 141 by a specimen holder 152. Depending on the experiment to be run, vessel 150 was filled with either blood or a buffer solution. The vessel 150 and the clot 151 were moved by a computerized x-y positioning a system 180 through a mounting 181 and a computer controller 182. Certain information regarding the effects of applied ultrasound were compiled with an ultrasound imaging device 160, formed with an imaging ultrasound transducer 161, coupled to a processor 162 for interpreting information received from transducer 161 and displaying an image thereof. Additional information was compiled through the use of a microphone 170 attached to tank 141, coupled to a frequency analyzer 171 through an amplifier 173, which also receives a trigger signal 172 from generator 120. Trigger signal 172 corresponds to transducer activation signal 121, so that only sound transmitted from microphone 170 when transducer 110 is activated will be analyzed.

It was determined that advantageous benefits can be achieved when ultrasound is applied at a pulse duration τ not greater than about 100 milliseconds (msec). A range of about 0.01 to 100 milliseconds is preferred. Also, pulse repetition periods T below about 1 second are preferred, as are pulse repetition periods in the range 1 millisecond to 1 second. Duty ratios $T/\tau \geq$ about 5, and preferably ≤ 8 are preferred.

Non-invasive therapeutic ultrasound can be practiced at a frequency of about 100 to 1000 KHz and far broader. Invasive-type (probe-based) therapeutic ultrasound can be practiced at a frequency range of 20 to 100 KHz and far broader. At a frequency of preferably 100 to 1000 KHz advantageous operating parameter include $T =$ about 1 to 100 milliseconds, preferably about 2.5 to 90 milliseconds and more preferably 2.5 to 75 milliseconds and/or $\tau =$ 0.01 to 2.0 milliseconds, preferably 0.02 to 1.1 milliseconds and more preferably 0.1 to 0.3 milliseconds. These parameters are particularly well suited for a non-invasive-type device, particularly one applying ultrasound at $I \geq$ about 750 W/cm², more preferably \geq about 1000 W/cm².

At a frequency range preferably of 20 to 100 KHz, advantageous operating parameters include $T \leq$ about 1000 milliseconds preferably \leq about 600 milliseconds, more preferably about 100 to 500 milliseconds and/or $\tau \leq$ about 100 milliseconds, preferably about 10 to 100 milliseconds, more preferably 20 to 60 milliseconds. These parameters are particularly well suited for use with an invasive-type device, especially one operated at a peak power output of over 10 watts, such as one operated at 10-40 watts, preferably 15-30 watts. When pulse parameters are correctly selected, an invasive-type probe can be operated with substantially no cooling fluid.

Substantial benefits can be achieved by monitoring the progress of ultrasound treatment. This can be accomplished in at least two ways. In one embodiment of the invention, a microphone is placed on the body and cavitation can be detected by its audible signal. This can enable an operator to decrease power and/or change the pulse parameters until an acceptable audible signal is detected. Thus, by establishing a set of standardized acoustic signals produced by cavitation from a therapeutic ultrasound treatment, standardization in treatment can be improved. Furthermore, systems can be established which automatically reduce power or change pulse parameters if too high a cavitation signal is detected and automatically increase power or change pulse parameters if too low a signal is detected.

In another embodiment of the invention, a conventional ultrasound imaging transducer is used in conjunction with therapeutic ultrasound. An operator can observe not only a clot being broken up, for example, but the size and location of the cavitation cloud caused by the ultrasound. Thus, an operator can increase or decrease the power as needed, as described above. An operator can also pinpoint the location of the cavitation. Furthermore, it has been found that changing the pulse duration can change the size of the cavitation cloud. Accordingly, an operator can increase pulse duration in order to increase the size of the cavitation cloud or decrease the pulse duration to decrease the size of the cavitation cloud in order to insure a cloud of appropriate volume. Thus, if desired, the size of the cavitation cloud can be

increased to match the size of a clot and decreased if cavitation is occurring in an unneeded location.

In still another embodiment of the invention, computer recognition or other automated systems can detect the presence of cavitation, based on the signal received from the imaging transducer. This information can be used to automatically adjust parameters to optimize cavitation. Alternatively, this information can be used to display a cavitation level to a user or to sound a warning or even shut down the system if too much or too little (or none) cavitation is being produced.

In a preferred embodiment of the invention, the two transducers are concentric. The imaging transducer is preferably able to be rotated on the symmetry axis to give a long view, along the length of the vessel, which will appear as two parallel lines and a short axis, through the length of the vessel, which will appear as a ring.

The location of the clot can be determined through the ultrasound imaging transducer. To aim the transducer, it is positioned such that the vessel is parallel to one of the X-Y axis of the transducer movement system.

Referring to FIG. 31, a patient 3101 is seen receiving an ultrasound treatment via a transducer unit 3110. Unit 3110 contains an ultrasound imaging transducer concentric with an ultrasound generating transducer. Transducer unit 3110 is coupled via line 3111 to a control unit 3200, which is coupled to a display screen 3210. Display screen 3210 displays the image from the display transducer. By monitoring display screen 3210, an operator can determine the size and location of a cavitation cloud 3301 with respect to a clot 3302 in a vessel 3303. Thus, the size and location of cavitation 3301 can be matched to clot 3302 and to vessel 3303.

The following examples illustrating the non-invasive application of ultrasound were conducted in a water tank with a system having the general construction shown in FIG. 1A. These examples are provided for purpose of illustration only, and are not intended to be construed in a limiting sense.

Example 1

The transducer was operated at a frequency of 750 KHz, at a pulse duration of $\tau = 20 \mu\text{s}$, a pulse repetition period of $T = 74 \text{ ms}$ and a potential of 46 V. The hydrophone output was measured in decibels as a function of transversal displacement in mm along the Y axis, parallel to the transducer plane and corresponded to the predicted cigar shape at a distance of 5 cm from the transducer. The results are shown in FIG. 2.

Example 2

The hydrophone response at the focal point both above and below the cavitation threshold was measured. Referring to FIG. 3, it can be seen that when $\tau = 20 \mu\text{s}$ and $T = 74 \text{ ms}$ and transducer input was increased above about 160 volts, the effects of cavitation can be determined by a decrease in hydrophone response at the focal point, as energy is absorbed before the focal point, leading to a decrease of sound energy at the focal point itself.

Example 3

The effects of pulse duration on cavitation were measured by operating the transducer at an input potential of 180 V, $T = 75 \text{ ms}$ and measuring hydrophone output in a water filled tank at $\tau = 1100 \mu\text{s}$ (curve 51 in FIG. 4) and $20 \mu\text{s}$ (curve 52 in FIG. 4). As shown in FIG. 4, the longer pulse duration led to cavitation, whereas the shorter pulse duration exhibited no breakdown in focal depth. Accordingly, the initiation of cavitation depends not only on input voltage as has been believed, but also on pulse duration.

Example 4

The effects of pulse duration on cavitation were also analyzed for seven different pulse durations at 190 V and $T = 11 \text{ ms}$. Referring to FIG. 5, curve 61 is from a duration of $20 \mu\text{s}$, curve 62 is from a duration of $40 \mu\text{s}$, curve 63 is from a duration of $60 \mu\text{s}$, curve 64 is from a duration of $80 \mu\text{s}$, curve 65 is from a duration of $100 \mu\text{s}$, curve 66 is from a duration of $150 \mu\text{s}$ and curve 67 is from a duration of $200 \mu\text{s}$. Longer pulse durations were shown to be directly proportional to larger decreases in hydrophone output and consequentially, increased cavitation activity.

Example 5

The effects of increased voltage (increased power and intensity) on cavitation were analyzed more fully, by measuring hydrophone output as a function of Z-axis displacement at $T = 200$ ms and $\tau = 20$ μ s, at various input voltages. Referring to FIG. 6, curve 80 shows a theoretical plot at 190 volts, if no cavitation had occurred, curve 81 is from 100 volts, curve 82 is from 142 volts, curve 83 is from 155 volts and curve 84 is from 190 volts. Higher electrical input corresponded to higher amplitude and larger decreases in acoustic amplitude, compared to a theoretical prediction and hence, greater cavitation effect.

10 Example 6

The apparatus shown in FIG. 1A was used to dissolve a blood clot attached to the front of a wall taken from a bovine blood vessel. Referring to FIG. 7, the transducer was operated at a duty cycle $(T/\tau) = 8$ and an intensity of 1300 W/cm² and the pulse repetition period was varied over a range of about 0.5 to 27 ms. Optimal results were achieved in a range of about $T = 4$ to 10 ms, with peak clot dissolution efficiency at a pulse repetition period of about 8 ms and a pulse duration of about $\tau = 1$ ms. Thus, the operating parameters including a duty cycle of about 8 were deemed acceptable.

Example 7

20 The use of non-invasive ultrasound to lyse a clot attached to a vessel wall at parameters of $I = 1300$ W/cm² and $T = 8$ ms, for pulse durations ranging from about 0.07 ms to about 5 ms were performed and the results are presented in FIG. 8. The results show optimal clot dissolution at pulse durations of about $\tau = 0.5$ to 1.0 ms. It was also determined that increasing the pulse duration above about 2.3 ms began
25 damaging the vessel wall. It is believed that lysis is mechanical in nature and depends on various pulse parameters. Damage to the vessel (and to a probe in the case of invasive applications of ultrasound) is related to thermal effects, which are related to the accumulated energy transferred to a volume over time. Thus, by operating at a sufficiently short pulse duration, a clot can be lysed, without building up a
30 dangerously high amount of heat. It appears that operating above the cavitation

threshold, but less than about 50% of the pulse duration which can damage the vessel, can be both a safe and effective operating parameter.

Example 8

Referring to FIG. 9, the rate of clot mass dissolution as a function of ultrasound intensity at the focal area was analyzed with $T = 8$ ms and $\tau = 1$ ms. A non-linear increase in dissolution rate with intensity was observed with fastest dissolution at intensities in the 1200 - 1400 W/cm² range.

Example 9

The use of an ultrasound imaging system similar to system 160 shown in FIG. 1A provided additional information regarding the use of ultrasound for blood clot lysis. It is possible to visualize the clot during ultrasound application.

A bovine artery segment was filled with non-degassed PBS. The transducer was operated at frequency, $f = 650$ KHz, transducer excitation voltage, $U_{p/p} = 116$ volts, $T = 7$ ms and $\tau = 0.5$ ms. Bright reflection images corresponding to cavitation were seen only at the posterior artery wall. This indicated that the transducer was located too close to the vessel. After the transducer was moved away from the vessel, reflection spots, indicating cavitation within the vessel were observed, indicating proper positioning of the transducer.

After the transducer was moved still farther away, bright reflection corresponding to cavitation was observed only at the anterior artery wall, indicating that the transducer was located too far from the vessel. Thus, by combining conventional imaging ultrasound with non-invasive ultrasound lysis, it is possible to assure that the ultrasound focal point is at a desirable location within the body.

It has also been found that by changing the parameters, such as the pulse duration, it is possible to adjust the size of the cavitation cloud detected with the imaging system to a desired size, such as not greater than the size of the clot or vessel.

Example 10

A successful non-invasive clot lysis procedure was conducted under the following conditions: driving frequency = 650 KHz, transducer excitation voltage = 116 V, pulse repetition period, $T = 7$ millisecond and pulse duration, $\tau = 0.5$ msec.

Referring to FIG. 10A, an ultrasound image of a clot (right side) and buffer solution (dark left side) within a bovine vessel is shown. The focal point of the therapeutic transducer was advanced along the longitudinal axis of the artery segment from left to right. Ultrasound treatment was stopped at approximately the middle of the clot.

- 5 Referring to FIG. 10B, it can be seen that the dark section indicative of liquid has grown from left to right in the vessel, and the clot has been reduced in size from the ultrasound treatment.

Example 11

- Measurements of acoustic emission (microphone output) in the audible range were conducted as a manifestation of the degree of cavitation activity by placing a microphone on a water filled tank. Referring to FIG. 11, microphone output was measured as a function of ultrasound peak intensity at $T = 7$ ms, for both $\tau = 0.070$ ms and $\tau = 0.100$ ms. As shown in FIG. 11, a well defined threshold to the peak intensity was observed.

- 15 In addition, above the intensity threshold, the correlation between cavitation activity and intensity was linear. For data points corresponding to $\tau = 70$ μ s, virtually no microphone output was observed until intensity exceeded approximately 1100 W/cm^2 . For measurements made at $\tau = 100$ μ s, virtually no microphone output (cavitation) was observed until ultrasound peak intensity exceeded
20 about 600 W/cm^2 .

- As shown, cavitation activity increased with increased pulse duration. It was also observed that above the threshold, cavitation initiation was random, occurring in the range of $I = 600 - 2800 \text{ W/cm}^2$. However, if, for example, cavitation initiated at $I = 2,000 \text{ W/cm}^2$, microphone output would always be in the high range
25 relative to if cavitation initiated at $I = 800 \text{ W/cm}^2$. It was also determined that after cavitation is initiated, the intensity can be decreased. Although cavitation activity will decrease, cavitation was maintained at the intensity shown in FIG. 11.

- It was also determined that placing a microphone on the outside of the body of the subject receiving ultrasound treatments can provide an excellent method of
30 obtaining feedback regarding whether cavitation is occurring. Thus, if an operator is

applying ultrasound to a subject, he can watch or listen to a display from the microphone and determine whether cavitation is occurring under parameters where cavitation should be occurring. In addition, the microphone output can be fed to a data processor, which can display a warning signal or deactivate the ultrasound device if the device is fully powered, but cavitation is not being detected by the microphone. Also, the feedback can permit an operator to reduce power to the transducer to obtain the minimal amount of power needed to sustain cavitation. This procedure can also be performed while detecting cavitation with an ultrasound imaging transducer.

Example 12

Referring to FIG. 12, a comparison was conducted between cavitation activity produced in a buffer and in a clot for $T = 7$ ms and $\tau = 0.1$ ms. Both the threshold and slope of the increase of cavitation activity with intensity were different for the buffer solution and the clot. The linear correlation (R) of the buffer and clot plots were $R = 0.94$ and $R = 0.61$, respectively.

After cavitation had been initiated and detected either audibly or with an imaging transducer, the voltage can be decreased to decrease the ultrasound intensity, but maintain cavitation, i.e., it is an inertial phenomenon. Thus, in order to promote additional safety of operation, once cavitation of a clot has begun, the intensity can be decreased, often by as much as 50% or more to maintain cavitation within the blood vessel but diminish a chance to injure the vessel itself.

Cavitation in blood and buffer solution was analyzed for degassed and non-degassed media. Operating conditions were $T = 7$ msec and $\tau = 0.1$ msec. The cavitation threshold for a degassed medium is higher than in a non-degassed medium. Also, there was no difference in cavitation threshold between blood and the buffer solution for the parameters tested.

The cavitation threshold for non-degassed buffer and blood was in the range of 1000 to 1500 W/cm², closest to about 1200 W/cm². With respect to degassed buffer and blood, the cavitation threshold centered around 2000 W/cm².

The cavitation thresholds for non-degassed and degassed clots were also analyzed at $T = 7\text{ms}$ and $\tau = 0.1\text{msec}$. As with the above experiments, the cavitation threshold of a degassed sample was higher than the non-degassed sample.

Example 13

5 Referring to FIG. 13, the activity of cavitation in blood, as a function of ultrasound intensity, was analyzed at $\tau = 40\text{ }\mu\text{s}$ for pulse repetition periods of $T = 8\text{ ms}$, 16 ms , 20 ms , 30 ms , 40 ms , 50 ms , 70 ms , and 90 ms as shown in curves 751-758, respectively. As shown in FIG. 13, there is an intensity threshold for inducing cavitation and the threshold was inversely proportional to pulse repetition period. For
10 $T = 8\text{ ms}$, cavitation occurred at an intensity of about $I = 1250\text{ W/cm}^2$ and for $T = 90\text{ ms}$, cavitation was first observed at $I = 1750\text{ W/cm}^2$.

Example 14

Referring to FIG. 14, an experiment similar to that discussed with reference to FIG. 13 was performed, in which blood was tested at $\tau = 150\text{ }\mu\text{s}$ and pulse
15 repetition periods of $8, 16, 20, 30, 40, 50, 70$ and 90 ms , which are depicted by curves 451 through 458, respectively. Longer pulse repetition periods were associated with higher intensity requirements to initiate cavitation and higher cavitation activity.

Example 15

Referring to FIG. 15, the influence of pulse duration on cavitation
20 activity was analyzed. Shorter pulse durations were associated with greater cavitation activity. Also, a pulse repetition period $T =$ between about 10 and 50 ms created maximum cavitation activity for pulse durations from about $150\text{ }\mu\text{s}$ to about $700\text{ }\mu\text{s}$, correlating to duty ratios ranging from about 15 to 500 .

A buffer solution was subjected to ultrasound at an intensity of 2400 W/cm^2 . The pulse repetition period was varied from about $T = 5\text{ ms}$ to about 90 ms
25 for the following pulse durations: 0.100 ms (curve 151), 0.150 ms (curve 152), 0.250 ms (curve 153), 0.400 ms (curve 154), 0.700 ms (curve 155).

The experiment described above was repeated with pulse durations of 0.100 ms , 0.150 ms , 0.250 ms , 0.400 ms and 0.700 ms at an intensity $I = 2200\text{ W/cm}^2$.
30 The results are similar to those shown in FIG. 15, except that the cavitation activity

decreased slightly with the decreased intensity. Maximum cavitation activity occurred in the range $T < 50$ ms.

An experiment similar to that discussed above was performed at an intensity of $I = 2080 \text{ W/cm}^2$ at pulse durations of 0.100 ms, 0.150 ms, 0.250 ms, 0.400 ms. and 0.700 ms, respectively. Again, cavitation activity decreased with decreased ultrasound intensity and optimal pulse repetition periods were in the range $T < 40$ ms. Shorter durations were associated with higher activity. As ultrasound intensity and hence cavitation activity decreased, the width of the range of optimal pulse repetition periods also decreased.

An experiment similar to that discussed with reference to FIG. 15 was performed, in which ultrasound intensity was set at $I = 1800 \text{ W/cm}^2$. Maximum cavitation occurred above $T < 30$ for all but experiments run at a pulse duration of 0.700 μs , which exhibited cavitation to about $T = 50$ ms.

Example 16

Another experiment similar to that discussed with reference to FIG. 15 was performed, except that the medium tested was blood, rather than a buffer solution. Referring to FIG. 16, the intensity was set at 2400 W/cm^2 and results are shown for pulse durations of 0.100 ms, 0.150 ms, 0.250 ms, 0.400 ms and 0.700 ms for curves 251, 252, 253, 254 and 255 respectively. The parameters for causing cavitation in blood were found to be different than those for causing cavitation in the buffer solution. For example, cavitation in blood was sustained over a much wider range of pulse repetition periods, to over $T = 100$ ms. Again, however, the shorter pulse durations exhibited higher microphone output.

Example 17

FIG. 17 shows cavitation as a function of pulse duration for a blood sample (curve 351) and a buffer sample (curve 352), at $T = 50$ ms and intensity $I = 2400 \text{ W/cm}^2$. Optimal cavitation for the blood sample was in a pulse duration range of about $\tau = 100$ to $250 \mu\text{s}$ and a duty ratio of about 500 to about 200. It was evident that cavitation could still be achieved above $\tau = 700 \mu\text{s}$. For the buffer solution, the range

of most effective pulse durations was narrower, and ranged from about 80 to about 150 μ s. However, it was evident that cavitation would still occur above $\tau = 700 \mu$ s.

The experiment discussed with reference to FIG. 17 was repeated at $T = 8$ ms and the same intensity (2400 W/cm²). The shorter pulse repetition periods slightly decreased the cavitation activity for the blood sample and increased the cavitation activity for the buffer sample, relative to the values shown in FIG. 17 and caused the cavitation activity for the buffer samples to be more similar. Cavitation was sustained from $\tau = 50$ to 700 μ s. Accordingly, different materials will exhibit different activity with respect to different pulse repetition periods. Thus, it can be advantageous to lyse a clot with parameters which cause high cavitation in blood, and will have a less pronounced effect on the blood vessel.

Example 18

Referring to FIG. 18, the efficiency of clot lysis was analyzed by measuring percentage of clot weight loss as a function of ultrasound intensity for both a non-degassed (curve 551) and a degassed blood clot sample (curve 552). Lysis was performed with $T = 7$ ms and $\tau = 0.1$ ms, at $V_m = 15$ mm/min. Percentage of weight loss was determined by visual inspection and accordingly, the data are reasonable approximations. As shown in FIG. 18 the non-degassed clot was lysed at lower ultrasound intensities, with intensities above $I = 1600$ W/cm² judged effective on the non-degassed sample and above $I = 2200$ W/cm² on the degassed sample. Thus, the T and τ values and a duty cycle of 70 were deemed suitable.

Example 19

Referring to FIG. 19A, a clot was lysed at $I = 1900$ W/cm² at pulse durations of 100, 200 and 300 μ s. One hundred percent clot dissolution was achieved at 200 and 300 μ s. Referring to FIG. 19B, under the same conditions, except for a reduction of intensity to $I = 1400$ W/cm², optimum clot dissolution was achieved at $\tau = 200 \mu$ s, with clot lysis at reduced efficiency at $\tau = 100$ and 300 μ s. As shown, at lower intensities, high efficiency was achieved at $T/\tau = 35$, compared with $T/\tau = 70$ or 23.

Referring to FIG. 20A, at $T = 14$ ms and $V = 15$ mm/min and an intensity of $I = 1400$ W/cm², the results of curve 571, were achieved. Referring to FIG. 20B, when τ was set at 200 μ s, V was set at 10 mm/min and the pulse repetition period was varied from about 2.5 to 20, optimal clot dissolution was achieved at $T = 5$ ms, or $T/\tau = 25$, in a range of about 12 to 50, as shown by curve 572. Clot dissolution also be achieved above $T = 20$ ms.

Referring to FIG. 20C, curve 581, $T = 5$ ms, $\tau = 0.2$ ms and $V = 10$ mm/min, pulse duration was varied from 100 μ s to 300 μ s at an ultrasound intensity of 1300 W/cm². Optimal efficiency was achieved at $\tau = 200$ μ s, with the most efficient range from about 175 to 225 μ s. Lysis was effective above $\tau = 0.150$ ms.

Referring to FIG. 21, curve 582, intensity of ultrasound was varied from about 900 W/cm² to about 1700 W/cm². The cavitation threshold occurred at approximately 1250 W/cm² with maximum efficiency of intensities over 1300 W/cm² at $T = 5$ ms and $\tau = 0.2$ ms. Increasing intensity maintained full clot dissolution.

15 Example 20

Referring to FIG. 22, the efficiency of clot lysis was assessed by measuring the weight of unlysed clot after ultrasound application, as a function of ultrasound intensity. Parameters were $T = 5$ ms, $\tau = 0.2$ ms, $f = 650$ KHz, $V = 5$ mm/min and intensity ranged up to 2500 W/cm². Unlysed clot material was separated with an 80 μ m size filter. As shown in FIG. 22, above the threshold for clot lysis, only a small portion of the clot remained unlysed. At the parameters investigated, this intensity threshold was in the range 750 to 1250 W/cm².

The following examples present data illustrating from the application of ultrasound with a probe designed for the invasive application of ultrasound operated at about 44.4 KHz. Ultrasound was applied with a probe, similar to that depicted in U.S. Ser. No. 08/858,247, filed May 19, 1997 (the contents of which are incorporated herein by reference), having a proximal transducer coupled to an elongated transmission member with a distal tip constructed to cause cavitation within a blood

vessel when activated by ultrasound transmitted from the transducer through the transmission member.

A non-limiting embodiment of an invasive-type ultrasound probe is illustrated generally as probe 1200 in FIG. 22, and in a copending application entitled
5 COOLING SYSTEM FOR ULTRASOUND DEVICE under Application Serial No. 60/047,022, filed May 19, 1997, the contents of which are incorporated herein by reference.

Probe 1200 is formed with a tapered member 1225, formed with a proximal end 1229 of diameter A_i constructed to be coupled to a source of ultrasound
10 energy such as a transducer 1248. When coupled to a source of ultrasound energy, proximal end 1229 is preferably located at a displacement maximum relative to the standing ultrasound wave supported by the overall device. From proximal end 1229, tapered member 1225 tapers to a reduced diameter distal end of diameter A_r .

Proximal end 1229 must be large enough to receive sufficient energy to
15 treat a thrombus, occlusions and the like. However, in order to provide optimal flexibility, it is desirable to reduce the diameter of distal portions of probe 1200 as much as possible, without significant loss of energy, strength or guidability. Furthermore, the reduction in diameter is preferably accomplished in such a manner as to amplify, or increase the amplitude of, the ultrasound vibrations.

20 Ultrasound device 1200 is understood to operate in the resonant frequency mode; i.e., it supports a standing wave when energized by ultrasonic stimulation at proximal end 1229. Consequently, it is preferred that a cavitation tip 1250 is located at a displacement maximum (anti-node).

To dissipate energy lost as heat, a probe in accordance with the
25 invention can be bathed with a coolant. The coolant can be directed over and around the probe, for example, by incorporating a sheath 1245 around some or all sections of the probe. Sheathing 1245 may be affixed to the probe at one or more of the displacement nodes of the standing wave. Additional sheathing may be incorporated for providing a passageway for a guidewire or other auxiliary tool which may serve to

steer or position the device to its intended location. Sheathing 1245 is formed of a high-strength, thin-walled, low-friction material, preferably polyimide.

Probe 1200 includes a horn 1225, having a tapered section T and a first constant diameter section S, is constructed to be coupled to an ultrasound energy source. Ultrasound energy is provided by the controller at a power source 1246 via a coaxial cable 1247 to a quick disconnect 1249, which connects coaxial cable 1247 to transducer 1248. Transducer 1248 is intimately connected to horn 1225. Probe 1200 also includes a transmission member 1240 coupled to horn 1225 and a tip 1250 coupled to the distal end of transmission member 1240. Ultrasound energy sources disclosed in U.S. Patent No. 5,269,297, and in a copending application entitled FEEDBACK CONTROL SYSTEM FOR ULTRASOUND PROBE under Application Serial No. 60/046,938, filed May 19, 1997, the contents of which are incorporated herein by reference, are suitable.

Tip 1250 is coupled to three fine wires joining section 1240 and tip 1250 by means of three openings in tip 1250. In a preferred embodiment, the three openings in tip 1250 are spaced so as to form an equilateral triangle, concentric with the central axes of coupling tip 1250. Tip 1250 may also be provided with an opening for a guidewire, and a guidewire tube may be installed in the opening and extended proximally from the distal end. The fine wires may be separately sheathed, and any sheathing may extend between tip 1250 and a coupling joint. Wire 1240 may also be sheathed and the sheathing may be connected to the separate sheathing of the fine wires and may extend proximally to a coolant port through which coolant may be injected to bathe all or part of the transmission member.

The entire probe was placed in a straight configuration in a Plexiglas tube with an inner diameter of 3.5 mm and the tube was placed inside a water tank. A microphone was placed on the outside of the water tank and measured acoustic output which correlates to cavitation activity. The probe was operated in both continuous mode and pulse mode under various operating parameters and data was compiled.

Example 21

Referring to FIG. 24, at $T = 1000$ ms and $\tau = 500, 250, 750, 125, 875$,

164 ms, corresponding to curves 601-607 respectively and curve 608 corresponding to the probe activated in continuous mode, a cavitation threshold existed in the range 5 to 10 watts for pulsed mode of operation and non-degassed water.

Example 22

5 An additional experiment was run in non-degassed water at $T = 500$ ms and $\tau = 250, 125, 64$ and 32 ms. A control was also run in continuous mode. The results were similar to those shown in FIG. 24, with a threshold to cavitation in the range 10 to 20 watts and relatively no cavitation generated from operation in the continuous mode at up to 20 watts.

10 Example 23

 Referring to FIG. 25, an experiment similar to that discussed with reference to FIG. 24 was conducted, wherein non-degassed water received ultrasound from an invasive-type probe, but at $T = 250$ ms. Electric power was increased over the range 0 to 40 watts at $\tau = 125, 64, 32$ and 16 ms, corresponding to curves 125, 64, 32 and 16 ms, corresponding to curves 651, 652, 653 and 654, respectively. Curve 655 shows operation in the continuous mode. As shown in FIG. 25, an ultrasound threshold occurred at about 20 watts and there was essentially no cavitation generated from the continuous mode operation at this power level.

Example 24

20 Still another experiment was conducted, in which ultrasound was applied from an invasive-type transducer to non-degassed water at $T = 125$ ms and $\tau = 64, 32, 16$ and 8 ms. Cavitation initiated in the range 15 to 20 watts for the pulse mode of operation, but not in the continuous mode operation, demonstrating advantages of pulsed operation in accordance with the invention.

25 Example 25

 Referring to FIG. 26, the procedure discussed with reference to FIG. 24 was performed at $T = 64$ ms. Pulse durations of $\tau = 32, 16, 8$, and 4 ms are shown in FIG. 25 as curves 661, 662, 663 and 664, respectively. Continuous mode operation is shown as curve 665. The cavitation threshold occurred in the range 15 to 20 watts for

the pulsed mode of operation, but not the continuous mode of operation, demonstrating advantages of pulsed operation in accordance with the invention.

Example 26

Referring to FIG. 27, the above procedure was repeated at $T = 32$ ms and $\tau = 16, 8$ and 4 ms, corresponding to curves 671, 672 and 673, respectively. Continuous mode operation is shown by curve 674. A cavitation threshold occurred in the range of about 15 to 20 watts for pulsed operation, but with less overall cavitation activity than for some of the longer pulse durations. It is believed that the liquid medium requires a recovery period for optimum cavitation efficiency.

10 Comparative Example 27

The invasive-type probe was operated under 18 watts of power. A thermocouple in contact with the tip inside the tube provided real time data with respect to temperature. Referring to FIG. 28, the system was initially at 37°C , 10 ml/min of 24°C cooling water was pumped through the tube. As shown in FIG. 28, 15 this reduced temperature at the probe tip to approximately 24°C . At point 681, the probe was turned on and activated with 18 watts of power. This quickly raised the temperature to over 41°C (point 682).

At point 683, power was turned off and the temperature quickly returned to the cooling water temperature. At point 684, cooling water was turned off and the 20 probe returned to approximately 34.4°C . At point 685, cooling water was turned on and the temperature of the probe quickly returned to approximately 27° .

At point 685, the probe was turned back on and the temperature quickly rose to above 41°C . After the power was turned off, the temperature of the probe returned to the temperature of the cooling water and then returned to the temperature 25 of the tank after the cooling water was turned off.

Example 28

Considerably different results were achieved when the probe was operated in pulse mode at a duty cycle of 8 ($T = 250$ ms $\tau = 32$ ms) when 24°C cooling water at 10 ml/min was turned on, the temperature of the probe quickly 30 dropped to about 24°C . At point 691 power was turned on at a level of 20 watts. As

shown in FIG. 29, the probe temperature increased to only slightly over 27°C, for a temperature increase of only about 3°C. At point 682, power to the probe was turned off and at point 683, the cooling water was turned off. At point 684, cooling water was turned back on and at point 685, power to the probe was turned back on. The probe was operated at 18 watts until it was turned off at point 686. As shown, probe temperature only increased about 2°C.

Similar results were achieved at a duty cycle of 16 ($T = 250$, $\tau = 16$) (FIG. 30). At point 691, cooling water was turned on and at point 692, the probe was activated with 20 watts of power and turned off at point 693. As shown, probe temperature increased only 1 to 2°C. At point 694, cooling water was turned back on, the probe was turned on with 18 watts of power at point 696 and turned off at point 697. As shown, only a minimal increase in temperature occurred.

Tables 1 and 2 below provide evidence from additional experiments showing a minimal temperature rise when the probe is operated in a pulsed mode, particularly at a duty cycle ratio of 8 or more. In view of their minimal temperature increase using the described pulsing parameters in conjunction with the lower cavitation threshold and high cavitation activity, it is believed that invasive-type probes can be operated without cooling fluid and also, without a covering sheath. This will permit the use of substantially smaller guide catheters in view of an overall reduction in the outer dimensions of the probe. Another advantage is a considerable reduction in metal fatigue.

Table 1
Study on the temperature rise at different flow rates of the cooling buffer
and at different excitation modes.

#	Flow Rate	Duty Cycle	Power	Temp Rise	Max Temp
1	10	Continuous ³	18	16.8	41.7
2	10	Continuous	18	15.4	41
3	10	8	20	2.4	28.1
4	10	8	18	1.7	27.6
5	10	16	20	1.2	27.1
6	10	16	18	0.7	26.6
7	10	8	30	4.6	31.8
8	10	8	30	4.1	31.6
9	10	8	40	5.3	33.3
10	10	8	40	5.3	33.3
11	10	16	30	3.8	29.7
12	10	16	30	4.1	29.2
13	10	16	40	4.8	30.8
14	10	16	40	4.6	30.7
15	5	8	30	8.2	35
16	5	8	30	8.4	35
17	5	8	30	7.2	36.2
18	5	8	30	7.2	36.1
19	5	16	30	4.6	33.5
20	5	16	30	4.3	33.5
21	5	16	40	8.2	37.5
22	5	16	40	6.2	34.1
23	2.5	16	30	3.7	35.7
24	2.5	16	30	4.1	35.7
25	0	16	20	3.1	39.8
26	0	16	20	3.1	39.8
27	0	16	30	4.6	41.1
28	0	16	30	4.1	40.9
29	0	16	40	Destruction	—
30	10	Continuous	18	16.1	45.8
31	10	Continuous	18	16.8	44.3
32	10	Continuous	18	17.8	45.3
33	10	16	18	2.2	30
34	10	16	18	1.7	30.5
35	10	16	18	2.6	29.8
36	10	8	18	1.2	29.9
37	10	8	18	1.2	29.9
38	10	8	18	1.2	29.9
39	5	16	18	1.5	31.8

#	Flow Rate	Duty Cycle	Power	Temp Rise	Max Temp
40	5	16	18	1.7	32.1
41	5	16	18	1.5	31.9
42	0	16	18	2.4	39.6
43	0	16	18	2.4	39.6
44	0	16	18	2.6	39.8
45	0	16	18	2.6	39.8
46	0	16	18	2.6	39.8
47	0	16	18	2.6	39.8
48	10	16	18	1	28.8
49	10	16	18	1.2	29.1
50	10	16	18	1.2	29.1
51	5	16	18	1.5	31.4
52	5	16	18	1.7	31.4
53	5	16	18	1.7	31.4
54	10	8	18	1.2	28.9
55	10	8	18	1	29.1
56	10	8	18	1.2	29.4
57	10	Continuous	18	16.6	43.9
58	10	Continuous	18	16.1	43.6
59	10	Continuous	18	16.6	43.6

Table 2
Study on the temperature rise at different flow rates of the cooling buffer
and at different excitation modes.

#	Flow Rate ml/min	Duty Cycle	Pulse Rep. Period (mS)	Pulse Length (mS)	Power (watt)	Frequenc y (KHz)	Temperature Rise (grad)	Max Temp (grad)
1	10	Continuous	-	-	18	44.6	16.1	41.3
2	10	8	256	32	20/18	44.6	2.4/1.7	27.9
3	10	16	256	16	20/18	44.6	1.2/1.0	26.9
4	10	8	256	32	30	44.4	4.6	31.7
5	10	8	256	32	40	44.4	4.8	33.3
6	10	16	256	16	30	44.4	2.9	29.5
7	10	16	256	16	40	44.4	4.3	38
8	5	8	256	32	30	44.4	7.9	35
9	5	8	256	32	30	44.3	7.2	36.2
10	5	16	256	16	30	44.3	3.8	33.5
11	5	16	256	16	40	44.3	7	36
12	2.5	16	256	16	30	44.3	3.8	35.7
13	0	16	256	16	20	44.3	3.1	39.8
14	0	16	256	16	30	44.3	4.3	41
15	0	16	256	16	40	44.3	Destruction	-
16	10	Continuous	-	-	18	44.5	16.9	45
17	10	16	256	16	18	44.5	2.2	30
18	10	8	256	32	18	44.5	1.2	29.9
19	5	16	256	16	18	44.5	1.6	31.9
20	0	16	256	16	18	44.5	2.5	39.7
21	10	16	256	16	18	44.5	1.1	29
22	5	16	256	16	18	44.5	1.6	31.4
23	10	8	256	32	18	44.5	1.1	29.1
24	10	Continuous	-	-	18	44.5	16.4	43.8

Example 29

Referring to FIGS. 32A, 32B and 32C, it can be seen that the size of the cavitation cloud is related to pulse duration. For example, with the ultrasound generating transducer operating at 40 W/cm² average intensity in the focal area, the size of the cavitation cloud increased with increased pulse duration.

Referring to FIG. 32A, a small cavitation cloud 3201(a) can be seen with an ultrasound imaging transducer when the ultrasound generating transducer was operated at a pulse duration of 50 μsec. An operator viewing the procedure could determine that cloud 3201 was smaller than a clot 3302 attached to a vessel wall 3203 and decide to increase the pulse duration.

Referring to FIG. 32B, it can be seen that when the pulse duration was increased to 250 μsec, a medium sized cavitation cloud 3201(b) was generated. An operator could determine that cloud 3201(b) matched the size of clot 3202 and was within vessel 3203.

Referring to FIG. 32C, when the pulse duration was increased to 450 μsec, an operator monitoring the procedure with an ultrasound imaging transducer could observe that a large cavitation cloud 3201(c) was created not only within, but also outside vessel 3203. Therefore, an operator or even an automated system could detect that the cavitation cloud was undesireably large and reduce the pulse duration and cavitation cloud size to levels such as those shown in FIG 32B.

It is understood that the techniques described for the invasive and non-invasive application of ultrasound are also applicable to systems that promote or focus ultrasound energy to enhance the absorption of drugs, induce apoptosis in cells, and/or treat tissue, tumors, obstructions, and the like, within and without the body, systems to be utilized in or for laproscopic surgery, for ultrasonic scalpels, and to induce tissue hyperthermia such as for cancer radiation therapy, for example. Furthermore, drugs, such as streptokinase, urokinase, whose function or efficacy would be enhanced by ultrasound or that would enhance the application of ultrasound at the treatment site, may be infused within the coolant fluid for cooling the ultrasound probe or delivered

through a separate passageway within or without the ultrasound probe to the treatment site.

The following is a partial list of applications for pulsed ultrasound:

Clot lysis	Cell function manipulation (eg. migration, adhesion, etc.)
Plaque ablation	Drug delivery manipulation
Coagulation	Drug activity enhancement
Cancer treatment	Biological product manipulation (eg. genes, anti-sense DNA)
	Phonophoresis
Induction of Apoptosis	Molecule manipulation
Induction of Necrosis	Cavitation initiation manipulation
Liposuction/Lipolysis	Cavitation sustaining manipulation
Induction of Angiogenesis	Heat generation manipulation

5 It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained and, since certain changes may be made in the above composition of matter without departing from the spirit and scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

10 It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the invention which, as a matter of language, might be said to fall therebetween.

CLAIMS

What is claimed is:

1. A method of applying therapeutic ultrasound to a location within a body, comprising: activating a transducer with selected activation parameters to produce ultrasound and directing this ultrasound to a location within a body; monitoring the level of cavitation at the location within the body; adjusting the location of the ultrasound within the body or the activation parameters until a first level of cavitation is detected at a selected location within the body; and adjusting the parameters to change the level of cavitation at the selected location based on information obtained through said monitoring the level of cavitation.
2. The method of claim 1, wherein the ultrasound is directed to the location within the body in an invasive manner, with an ultrasound device which is inserted into the body.
3. The method of claim 1, wherein the ultrasound is directed to the location within the body with a non-invasive ultrasound producing device.
4. The method of claim 2, wherein the power to the transducer is reduced after cavitation is detected at the selected location.
5. The method of claim 3, wherein the power to the transducer is reduced after cavitation is detected at the selected location.
6. The method of claim 2, including the step of applying a microphone to the body, wherein said monitoring of the presence or lack of cavitation is performed with the microphone applied to the body.
7. The method of claim 3, including the steps of directing an ultrasound imaging transducer to the selected location, wherein the monitoring of the level of cavitation at the selected location is performed with the ultrasound imaging transducer.
8. The method of claim 7, wherein the ultrasound is delivered to the body in pulses and causes the formation of a cavitation cloud at the selected location and the duration of the pulses is adjusted to change the size of the cavitation cloud to a selected size in response to the monitoring.

9. The method of claim 4, wherein the ultrasound is causing cavitation and the amount of cavitation caused is reduced automatically if the amount of cavitation monitored exceeds a predetermined amount.

10. The method of claim 5, wherein the ultrasound is causing cavitation and the amount of cavitation caused is reduced automatically if the amount of cavitation monitored exceeds a predetermined amount.

11. A system for delivering ultrasound energy into a body, comprising:

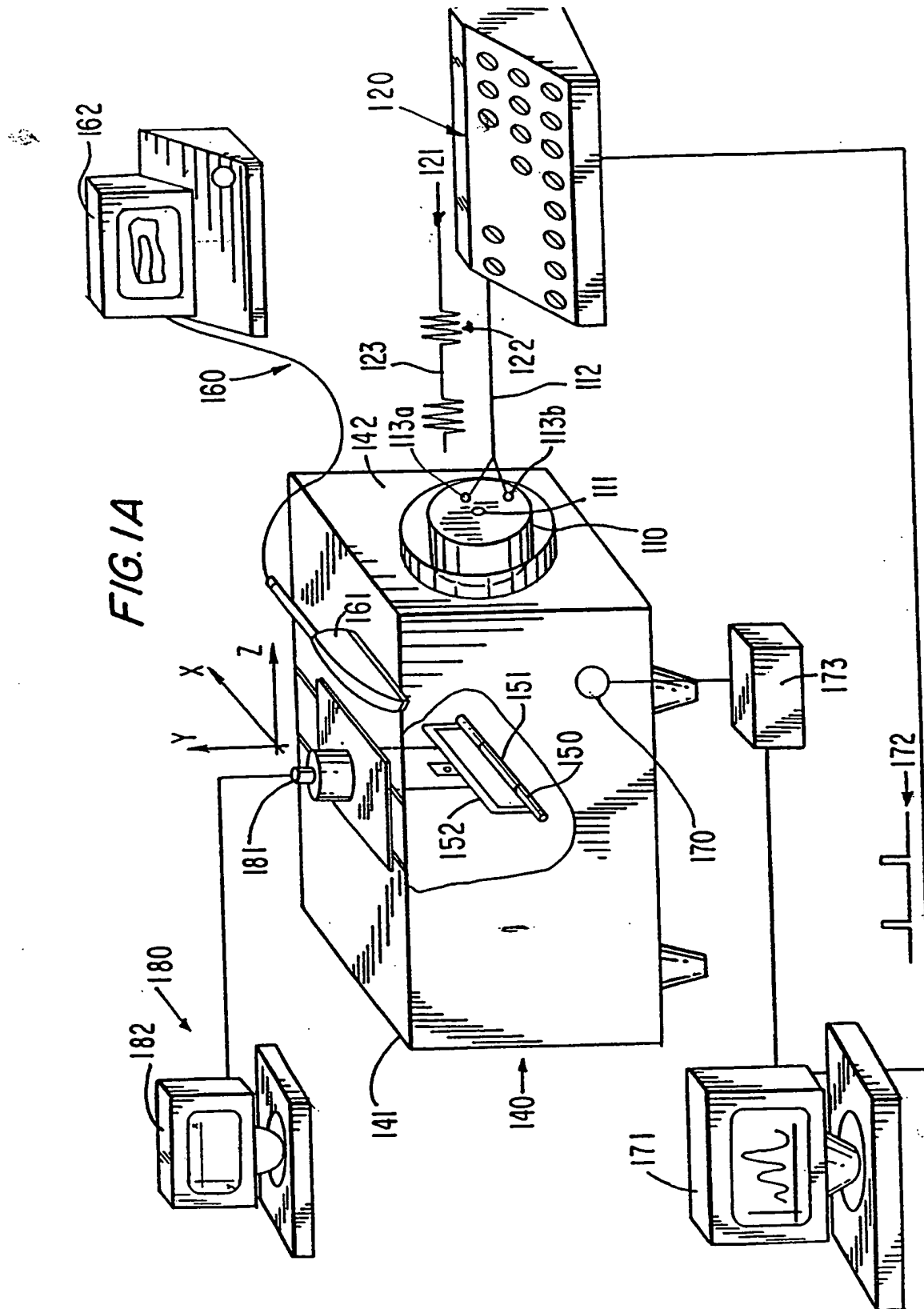
a signal generator, a transducer coupled to the signal generator, and a transmission member coupled to the transducer; the signal generator, transducer and transmission member constructed and arranged to transmit ultrasound to a location within the body by inserting at least a portion of the transmission member into the body; and

a sound detection device and a display capable of detecting the sound caused by cavitation within the body generated by ultrasound transmitted via the transmission member and displaying the presence of sound caused by the presence of cavitation.

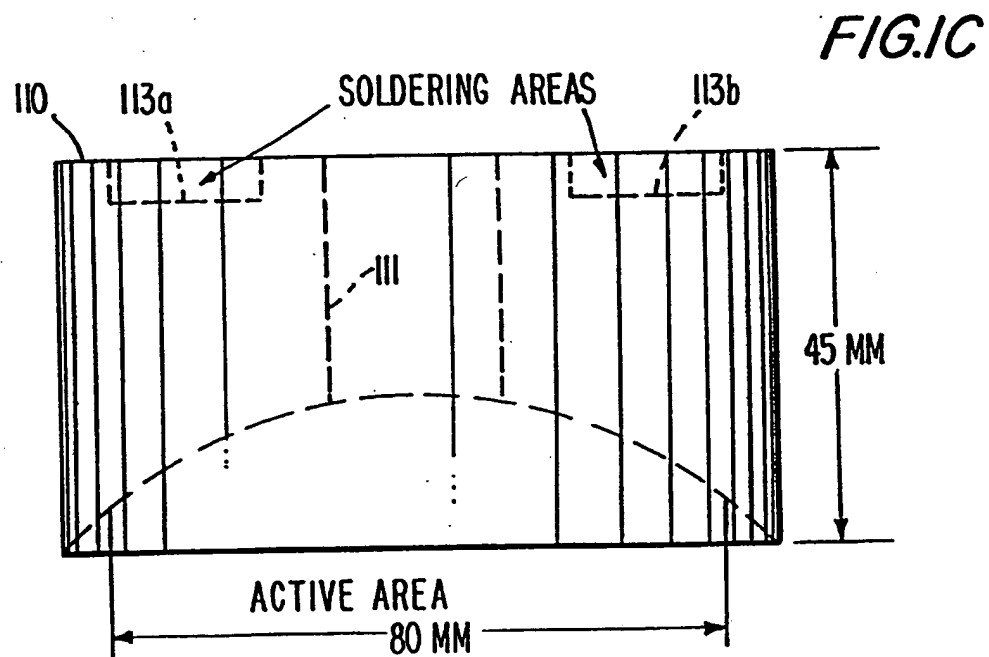
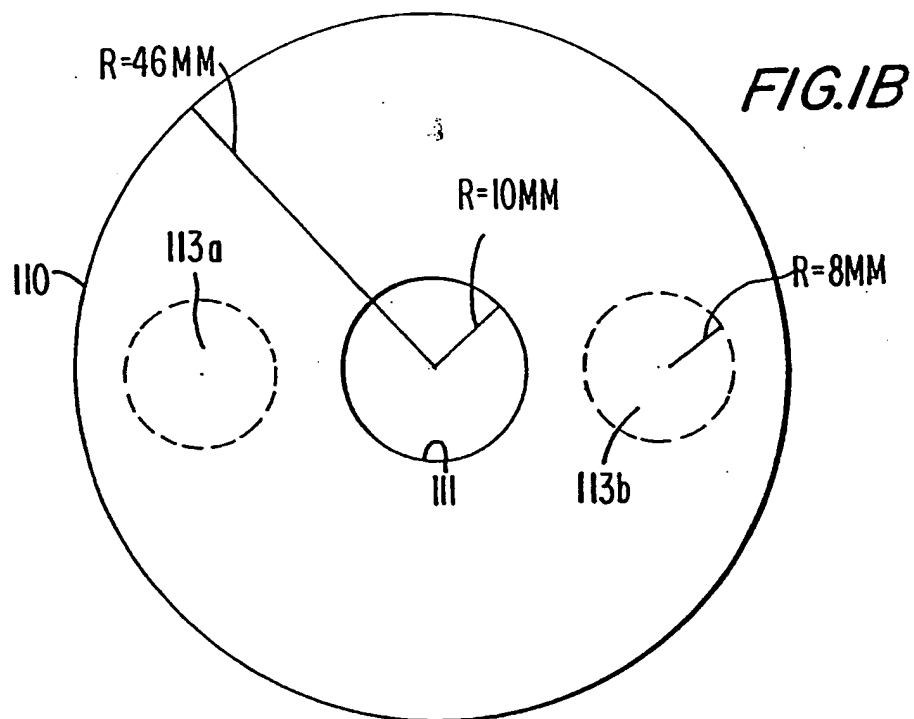
12. The system of claim 11, wherein the power of the transducer is decreased automatically when the sound detected exceeds a predetermined value.

13. A system for delivering ultrasound into a body, comprising:

a transducer unit formed with an ultrasound producing transducer capable of transmitting ultrasound into a body non-invasively; an ultrasound imaging transducer, the imaging transducer adapted to detect cavitation caused within a body by ultrasound from the ultrasound transducer and generating a signal responsive to the presence and intensity of cavitation caused within the body; a control unit responsive to the signal from the imaging transducer, adapted to generate a control signal when the signal from the imaging transducer indicates ultrasound detected at an intensity above a preselected level; the system constructed so that the power of the ultrasound transmitted to the body is reduced in response to the control signal.



2/36



3/36

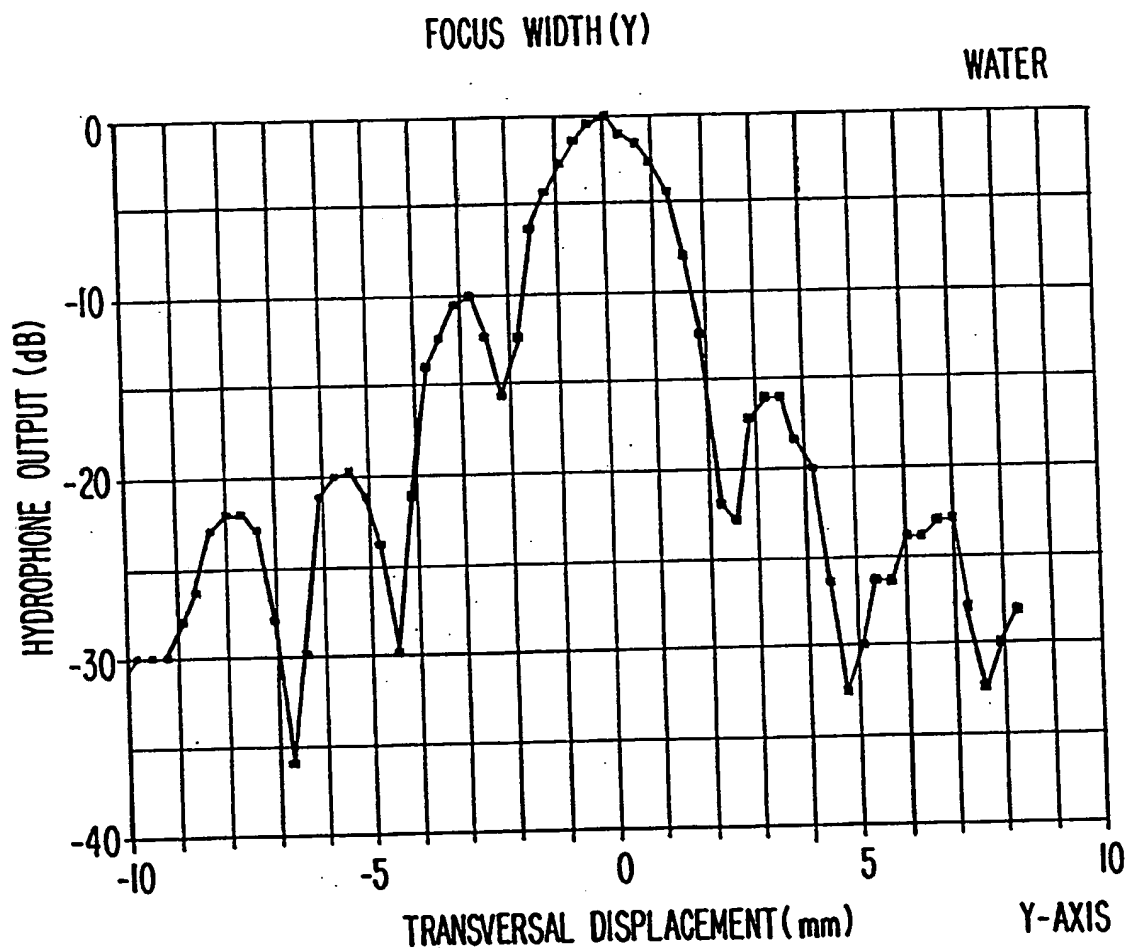
FIG. 2 $t = 20 \mu\text{s}, T = 74 \text{ ms}, 46\text{V}$

FIG. 3

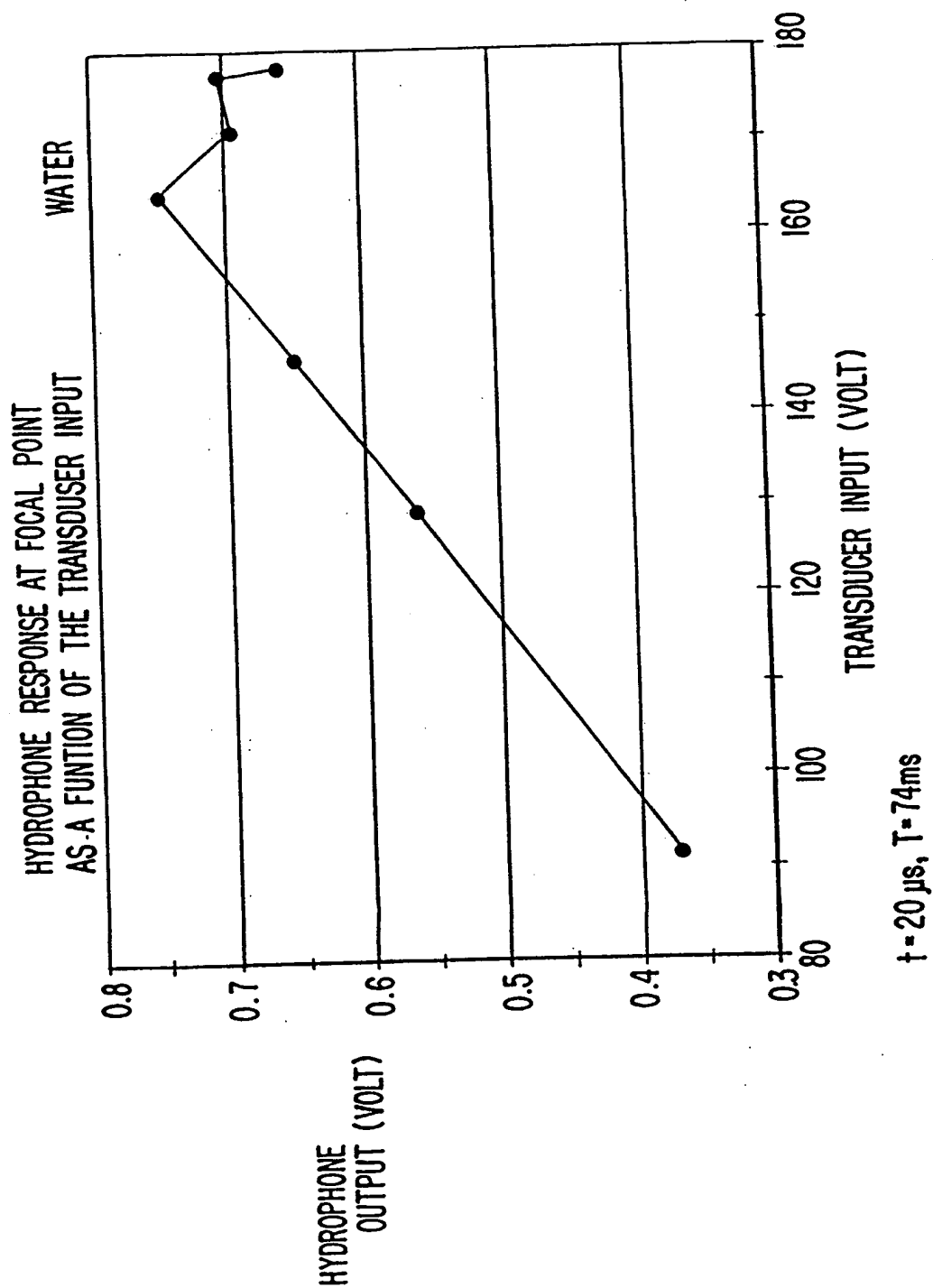


FIG. 4

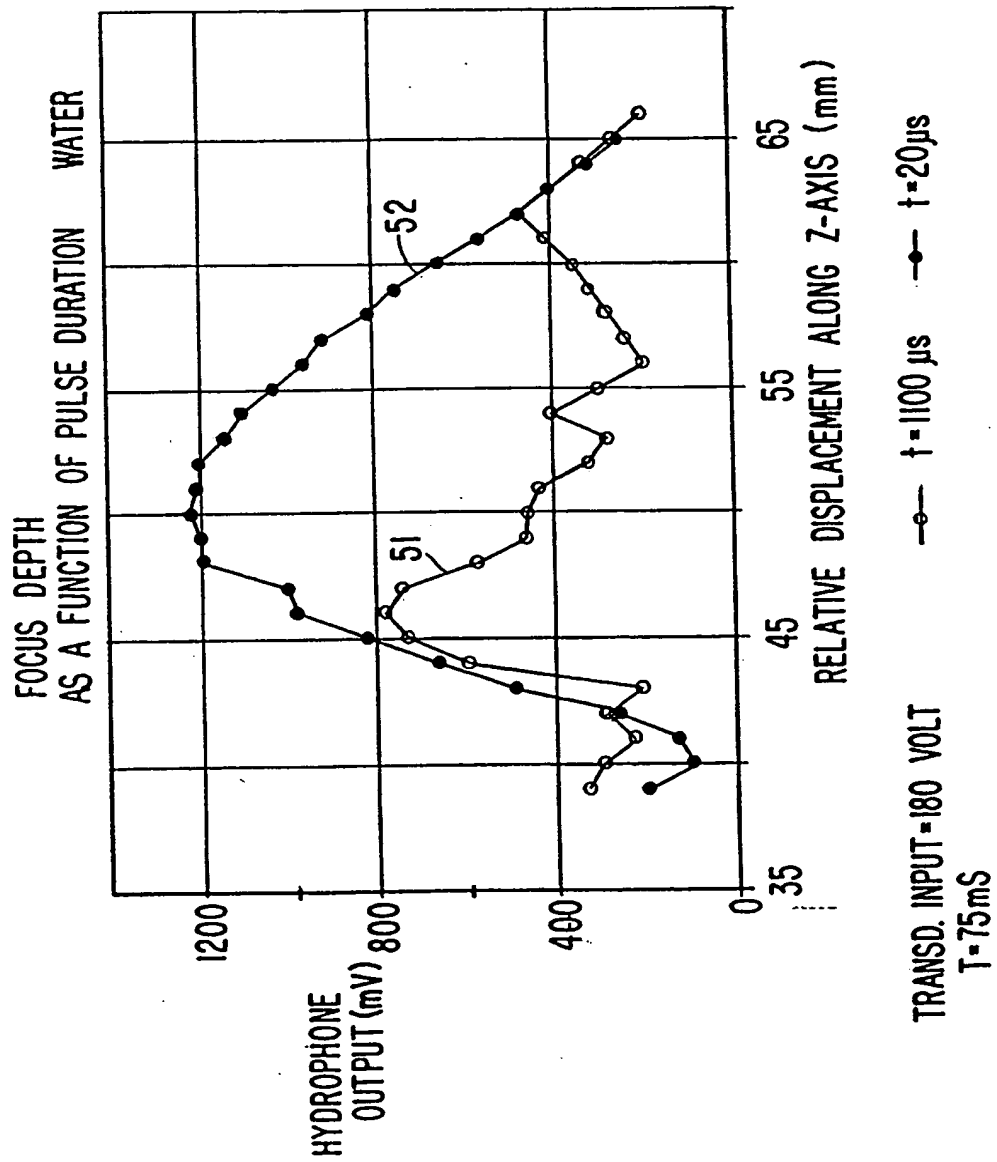


FIG. 5

WATER

PULSE
DURATION

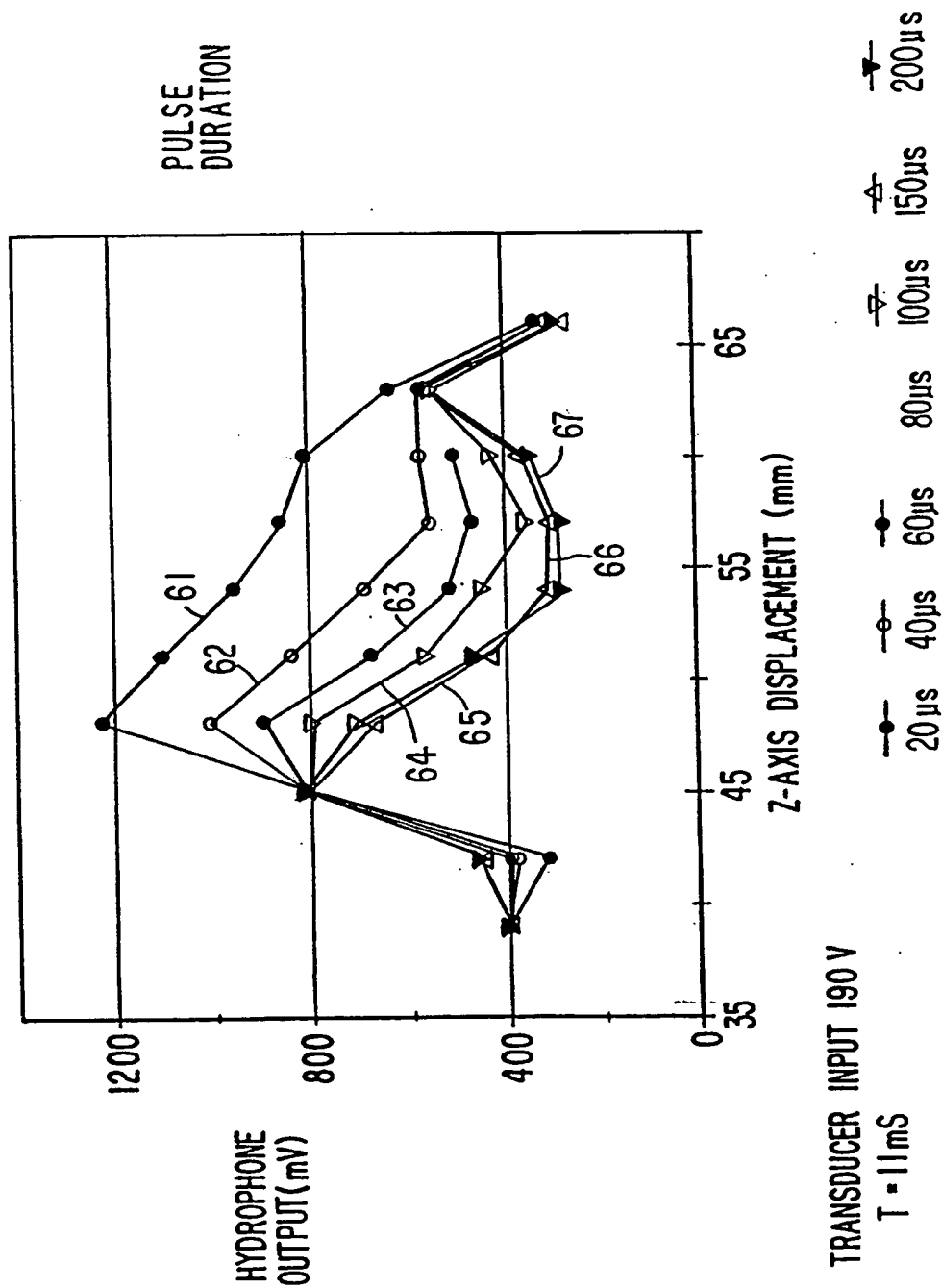
ACOUSTIC FIELD DISTRIBUTION AS A FUNCTION OF PULSE DURATION

HYDROPHONE
OUTPUT (mV)

Z-AXIS DISPLACEMENT (mm)

TRANSDUCER INPUT 190 V

T = 11ms



7/36

WATER
FIG. 6

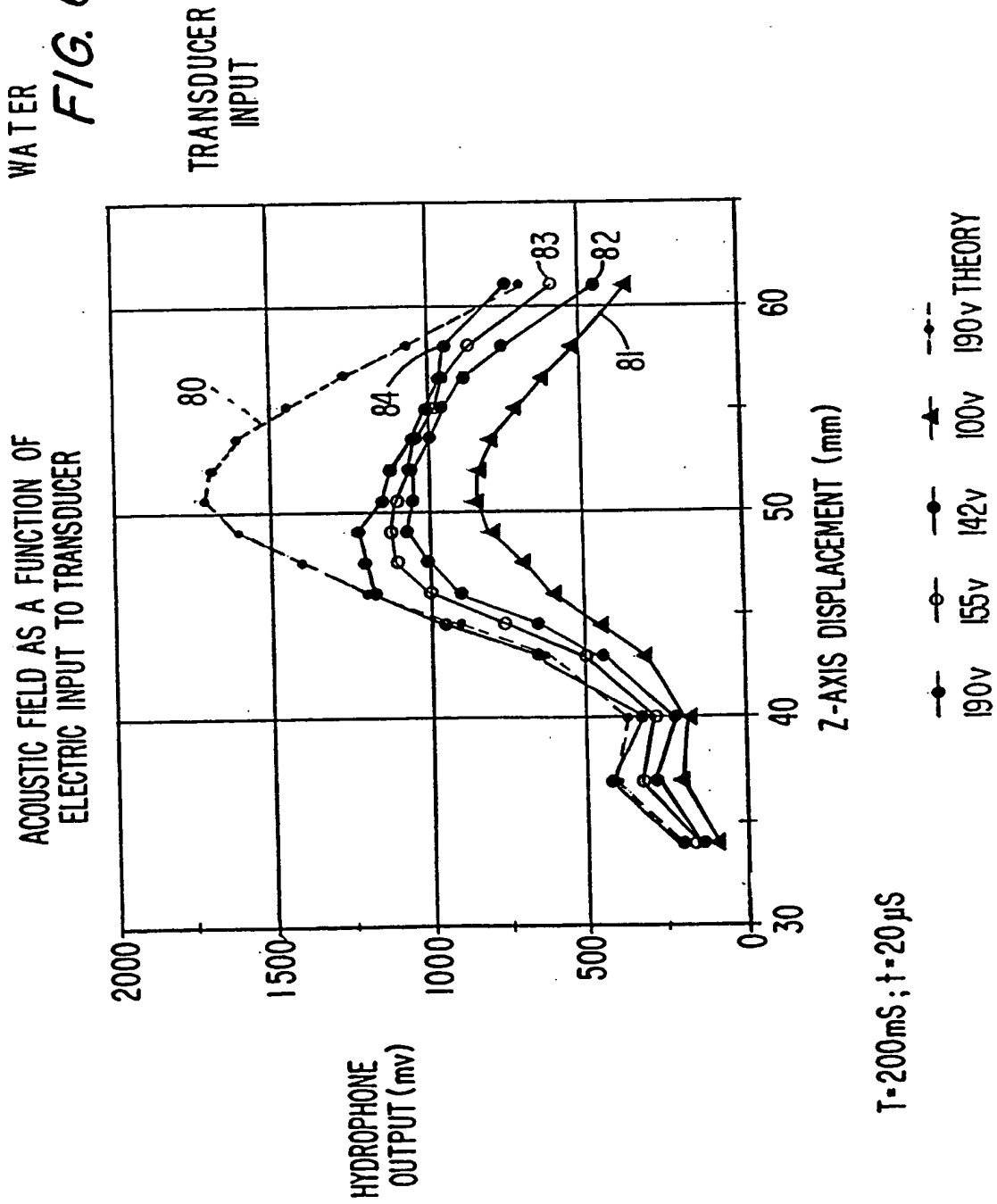
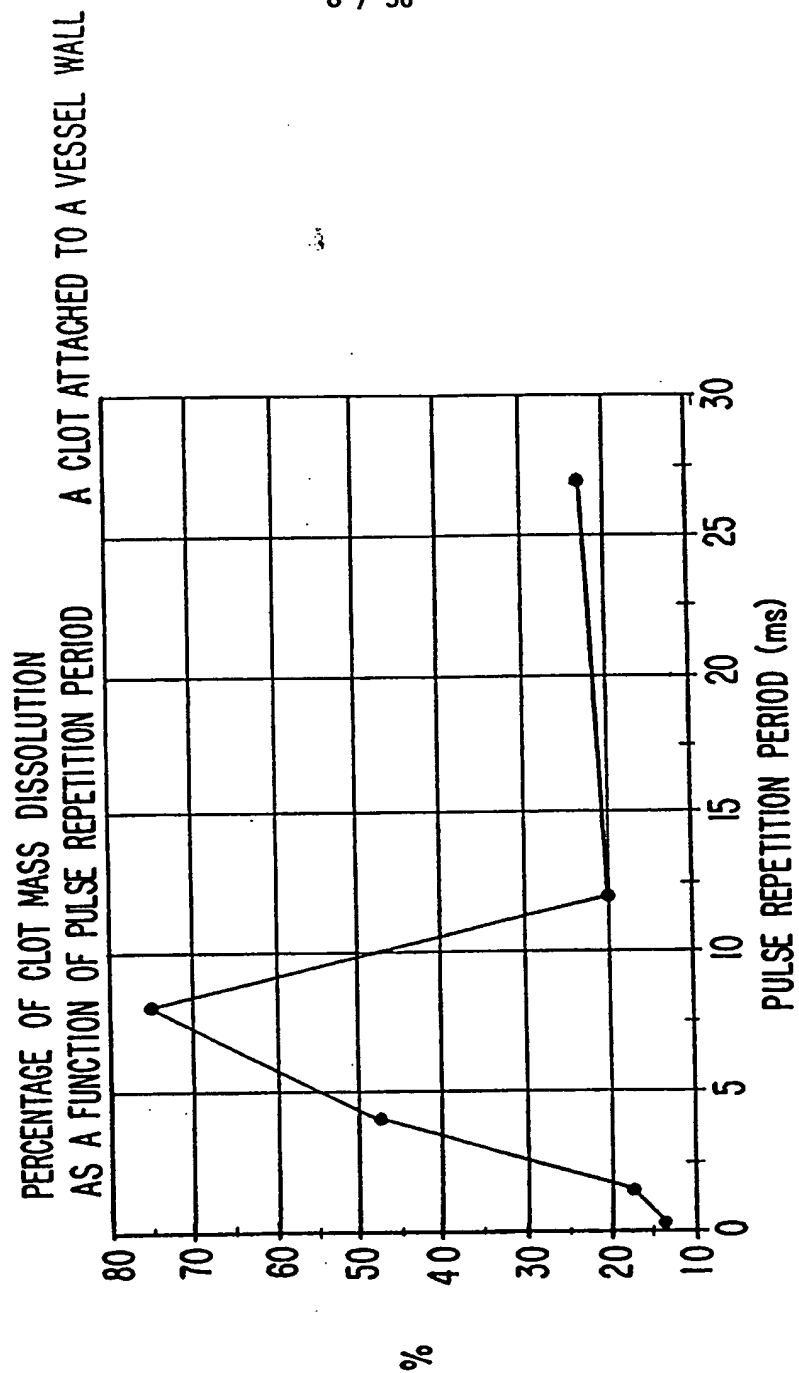


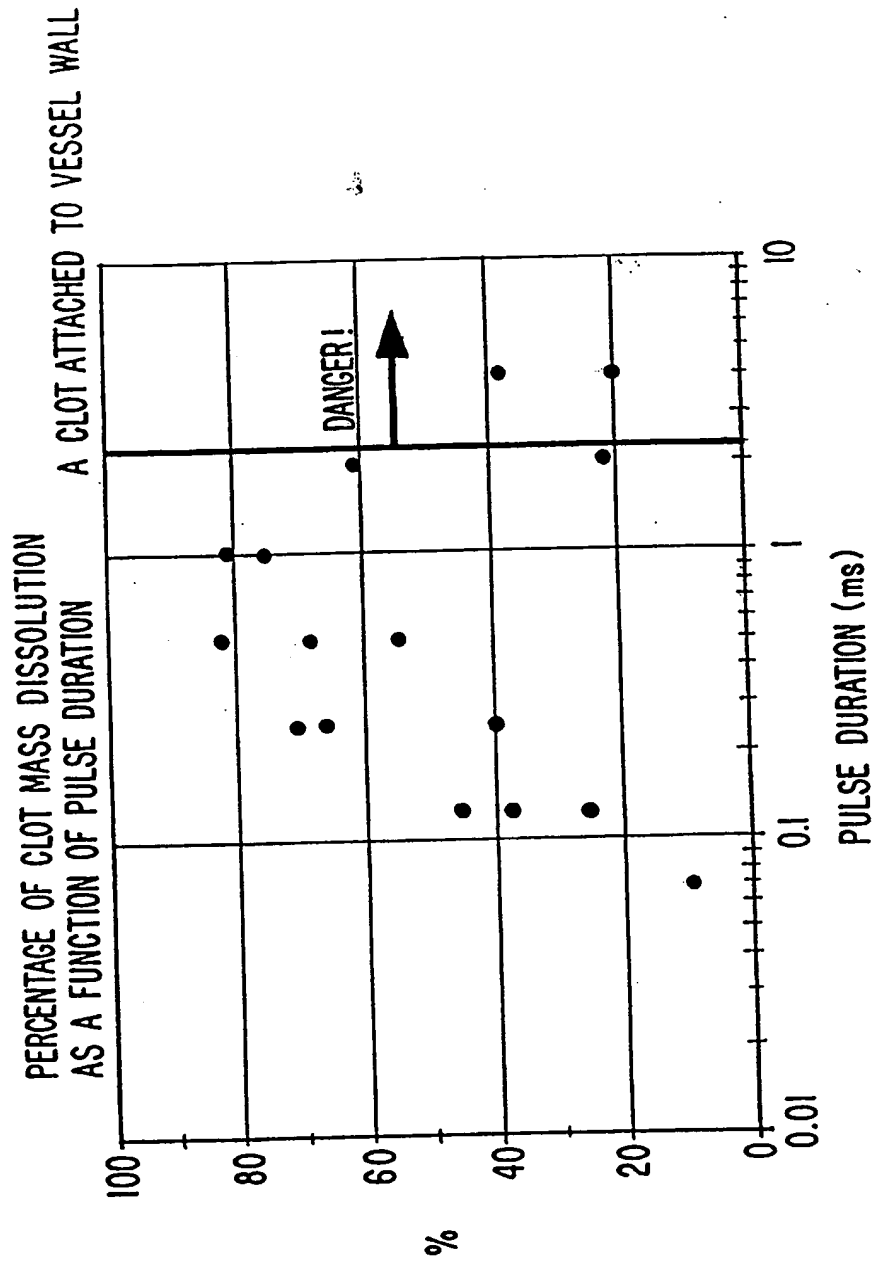
FIG. 7



DUTY CYCLE (T/t) = 8
INTENSITY = 1300 W/cm²

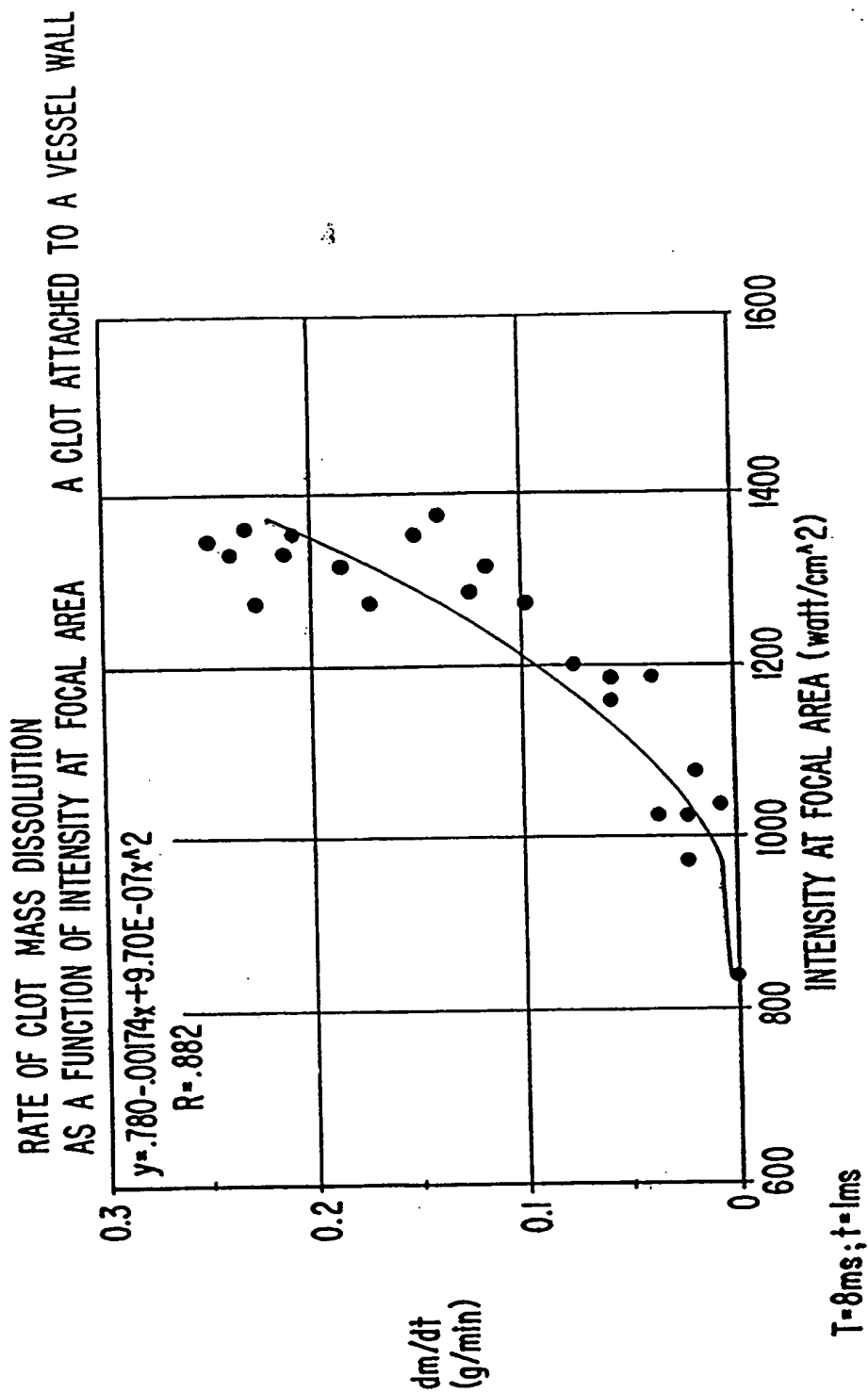
9/36

FIG. 8



$T = 8 \text{ ms}$
 $I = 1300 \text{ W/cm}^2$

FIG. 9



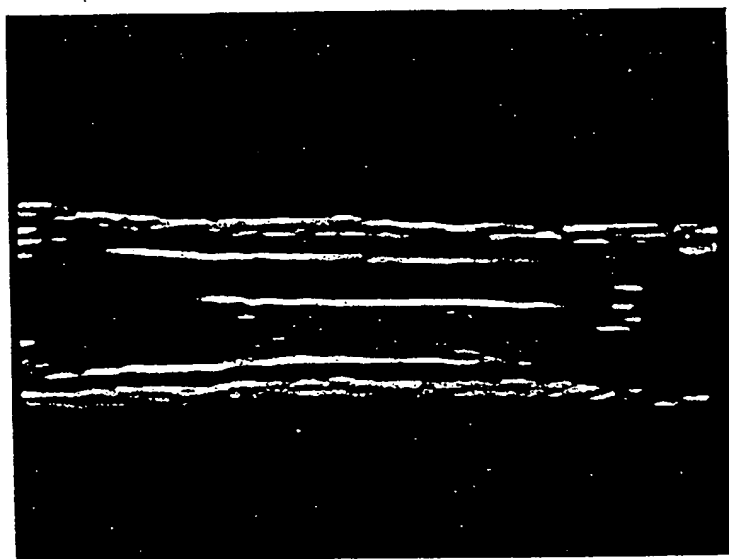


FIG. 10A

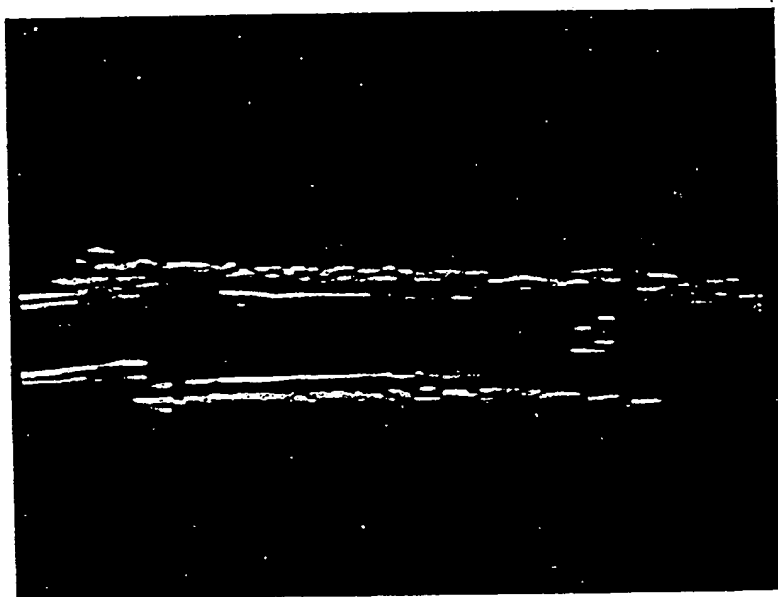
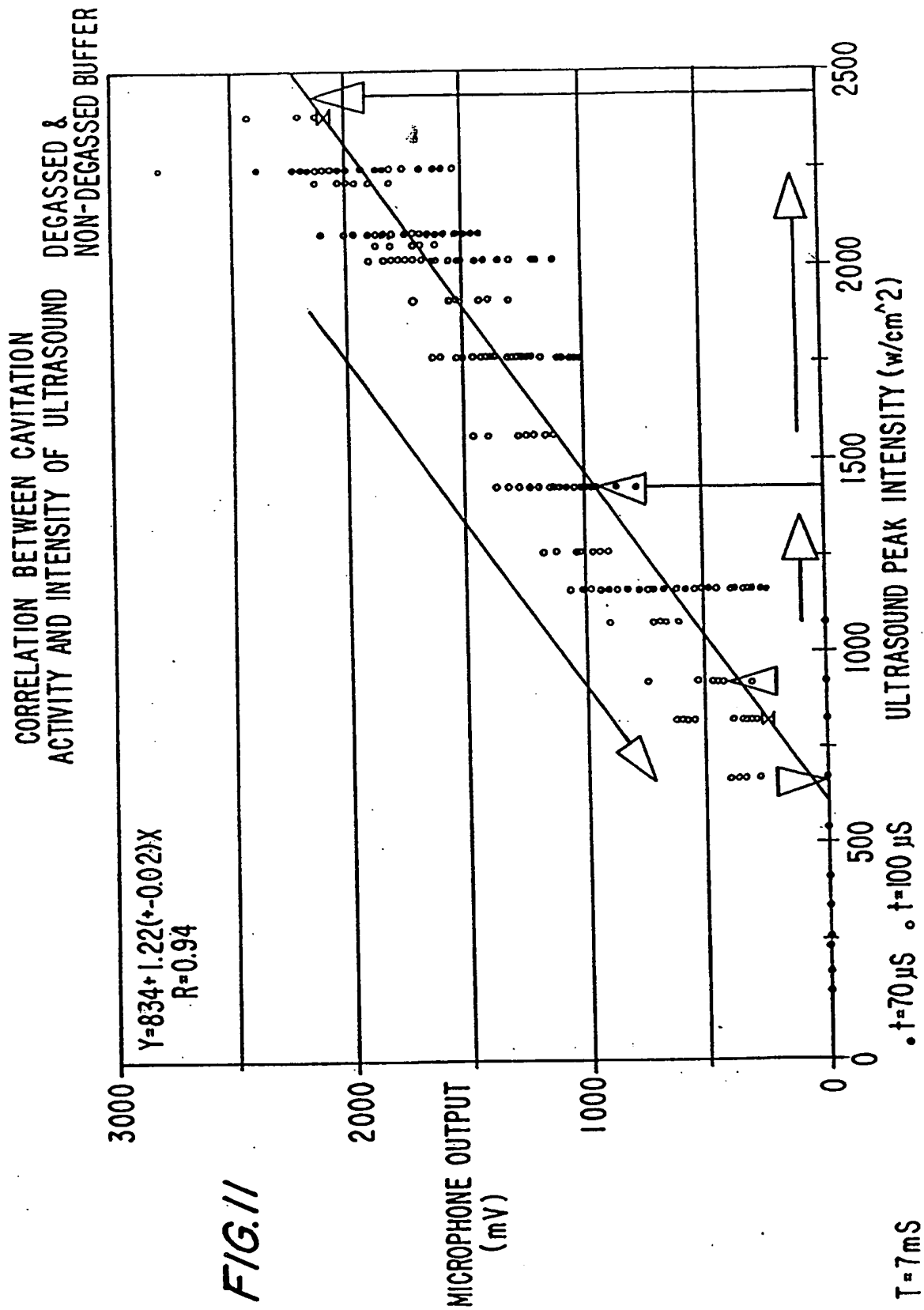
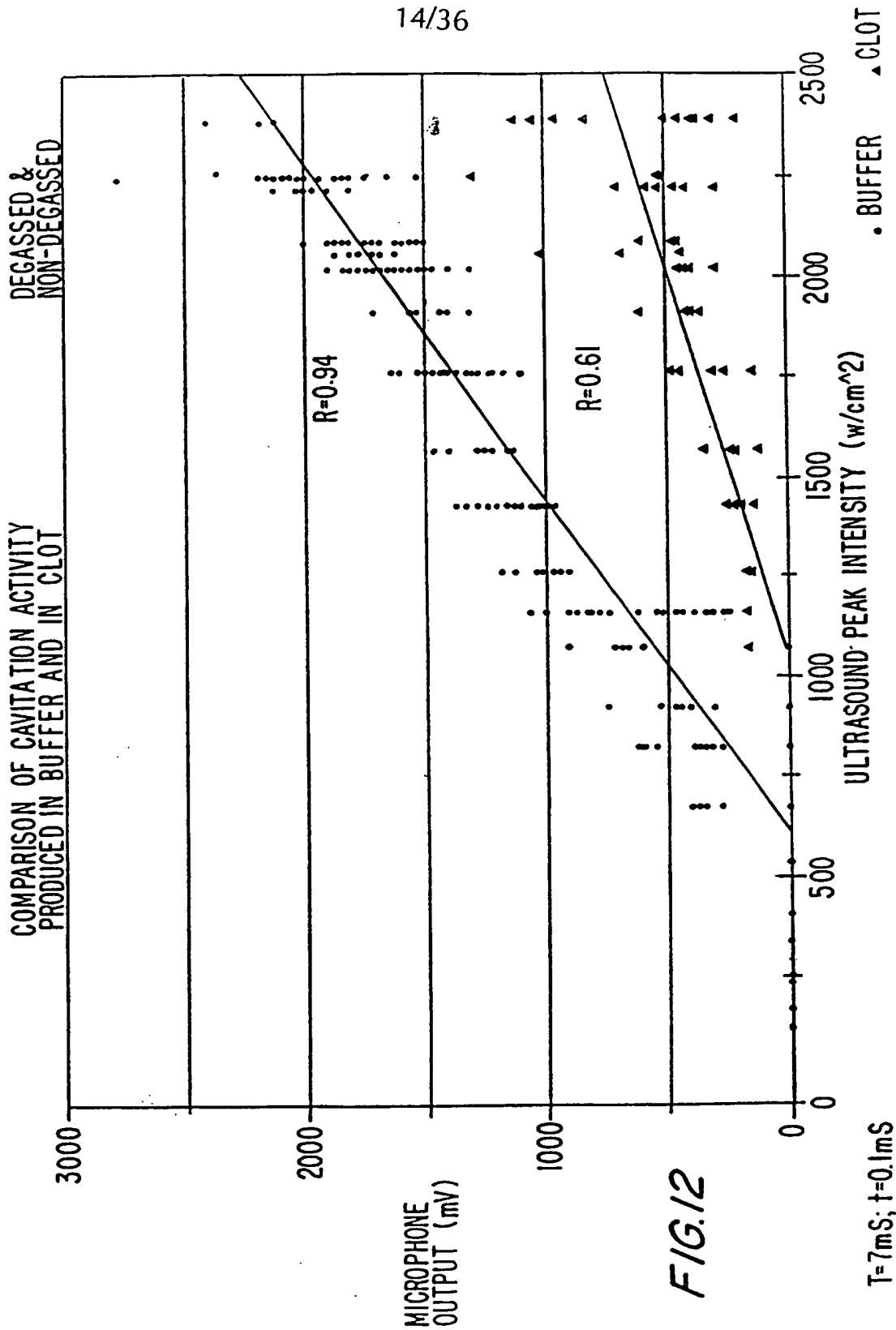


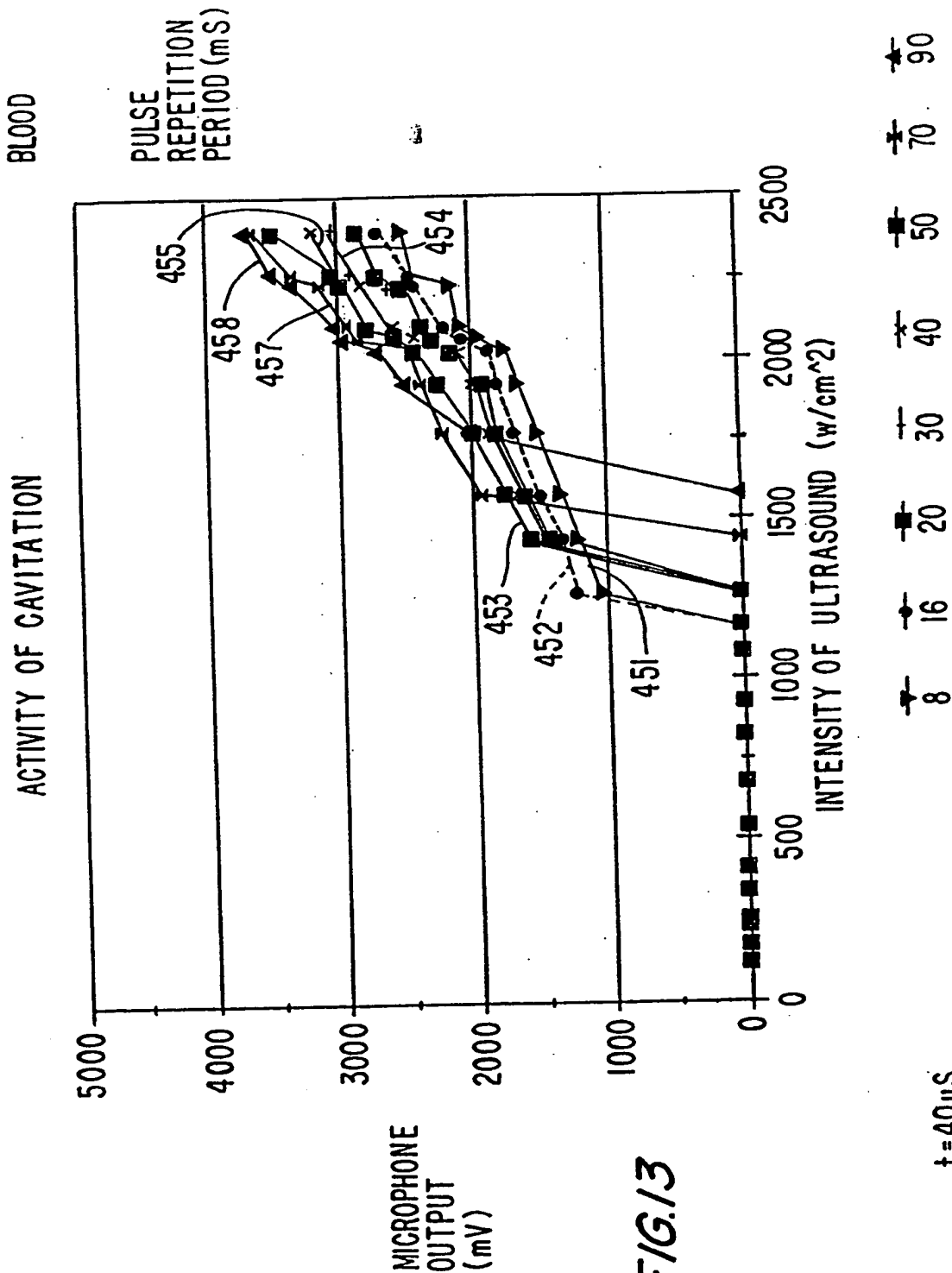
FIG. 10B



14/36



15/36



16/36

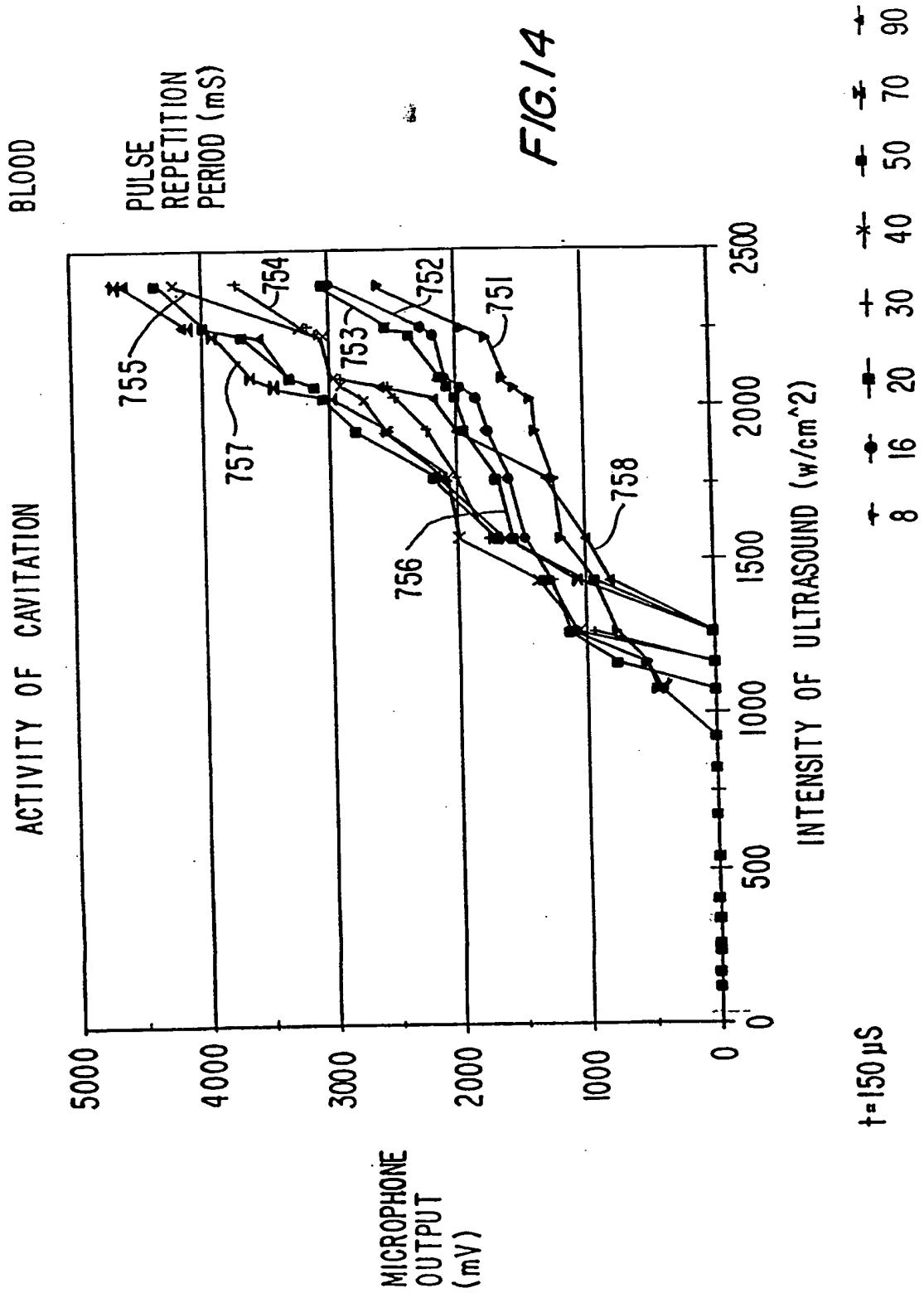
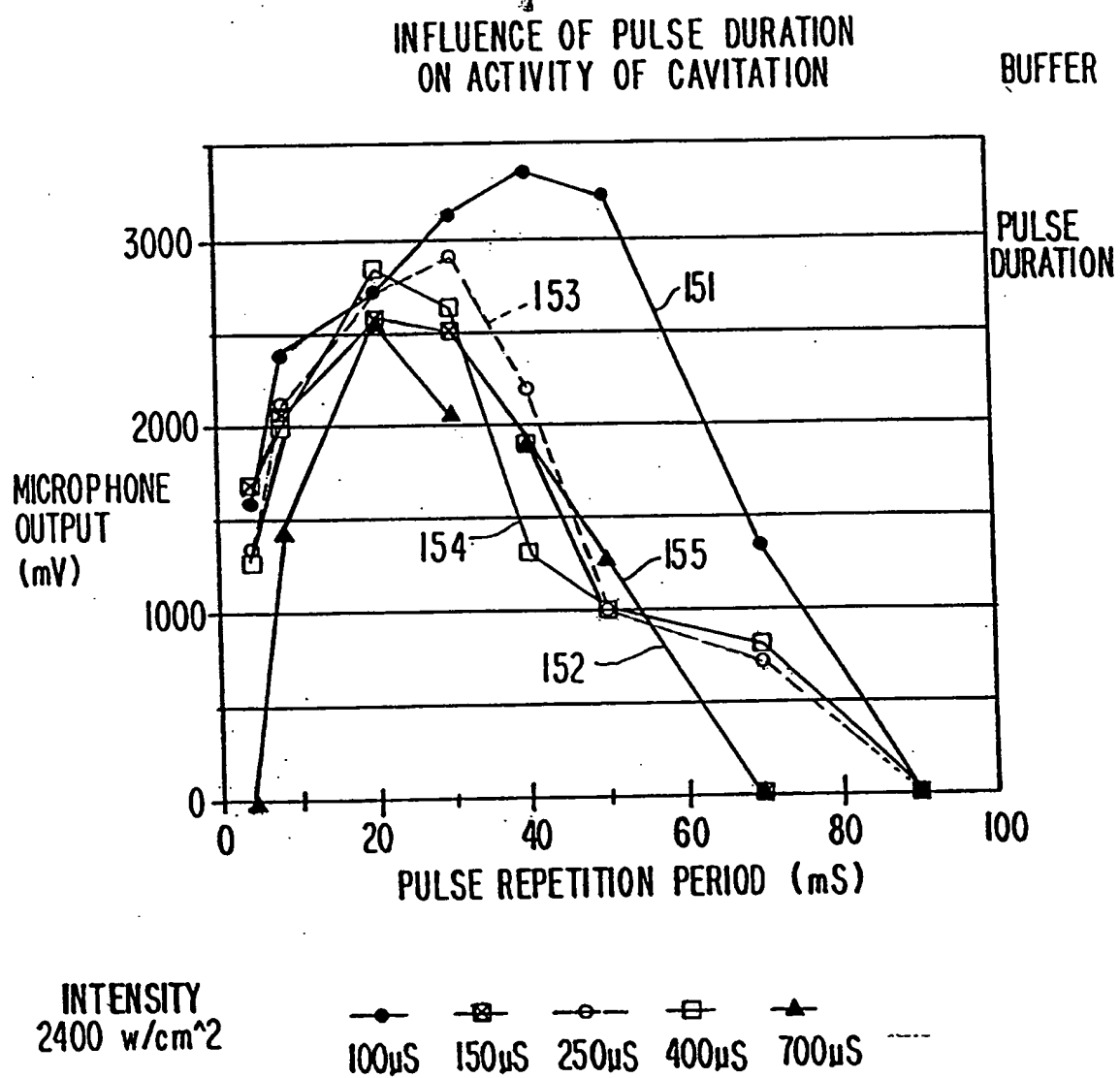
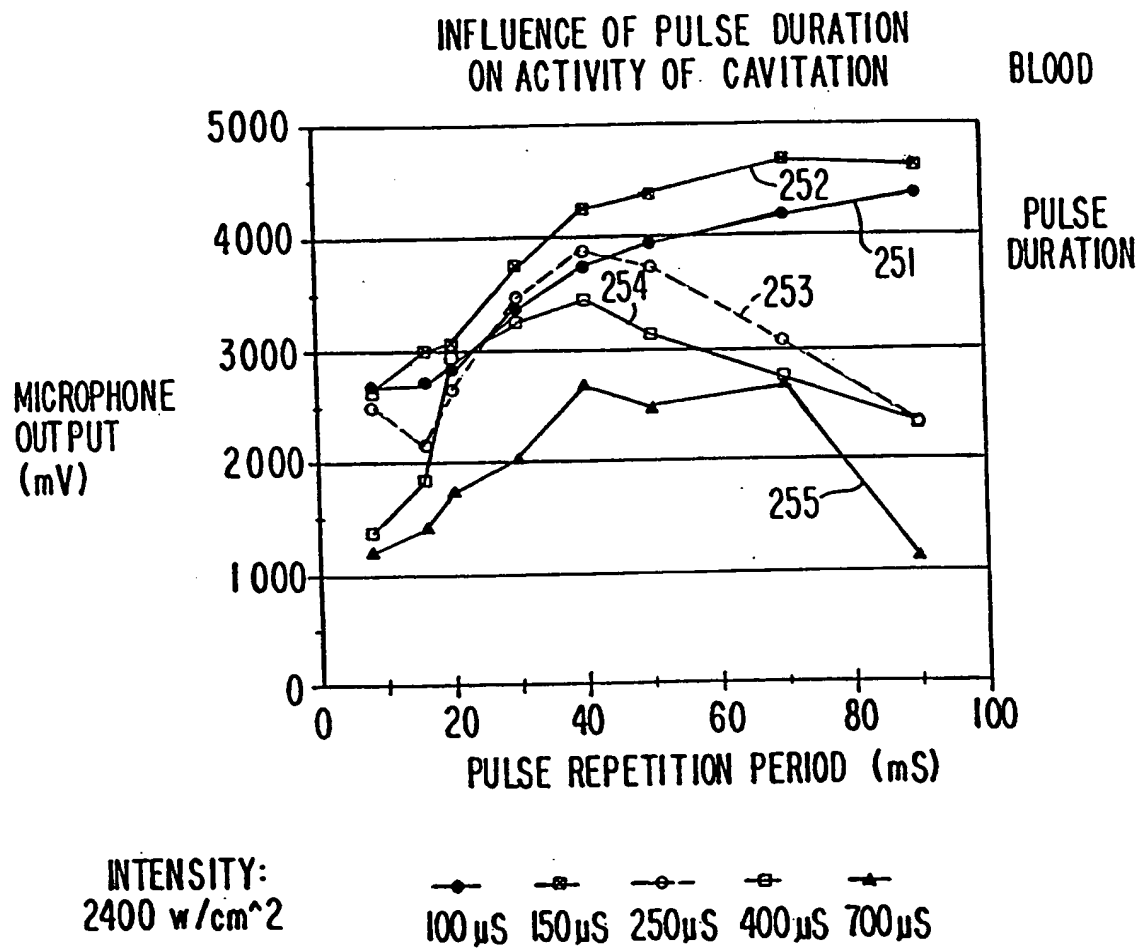


FIG. 14

17/36

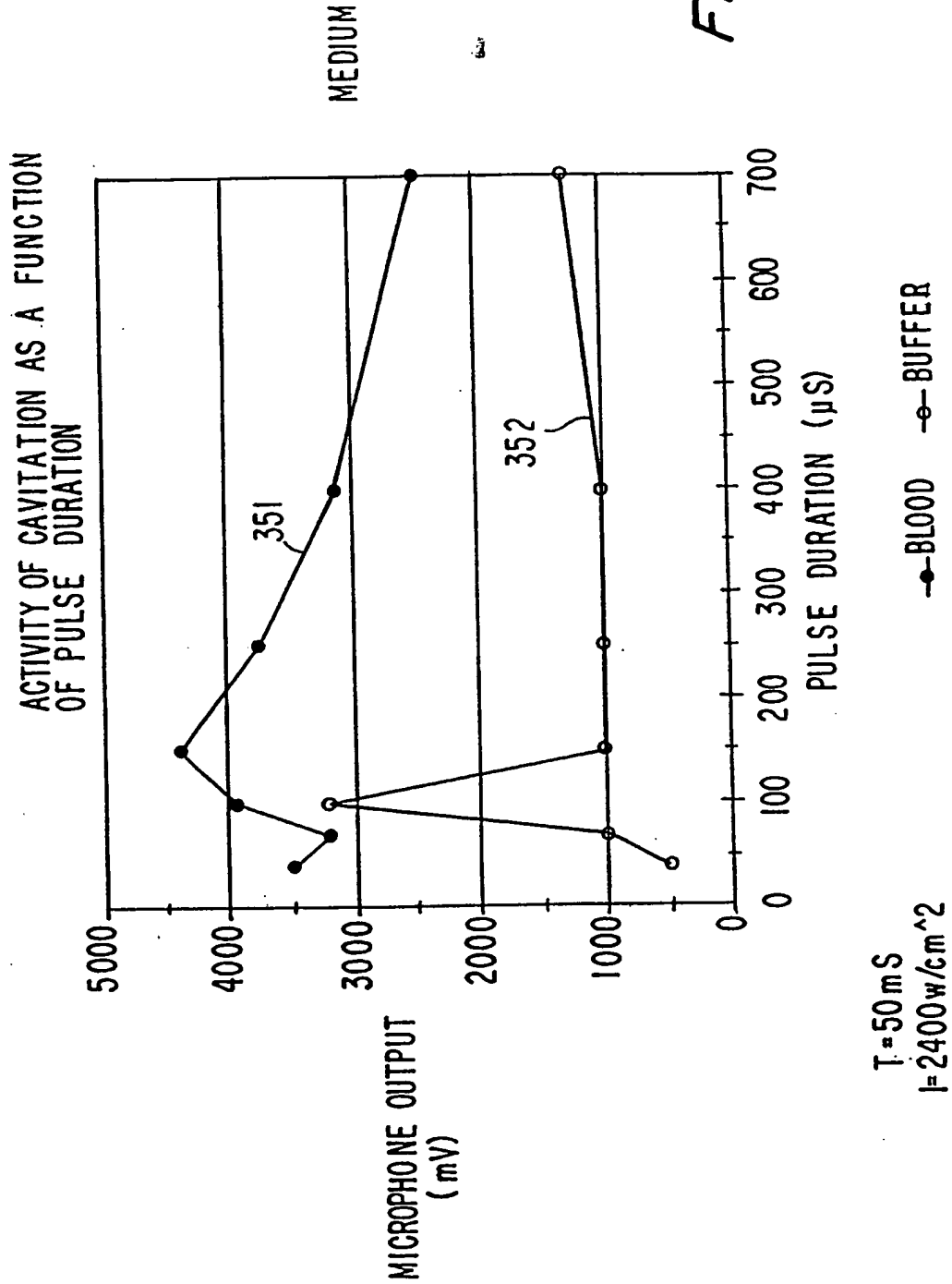
**FIG.15**

18/36

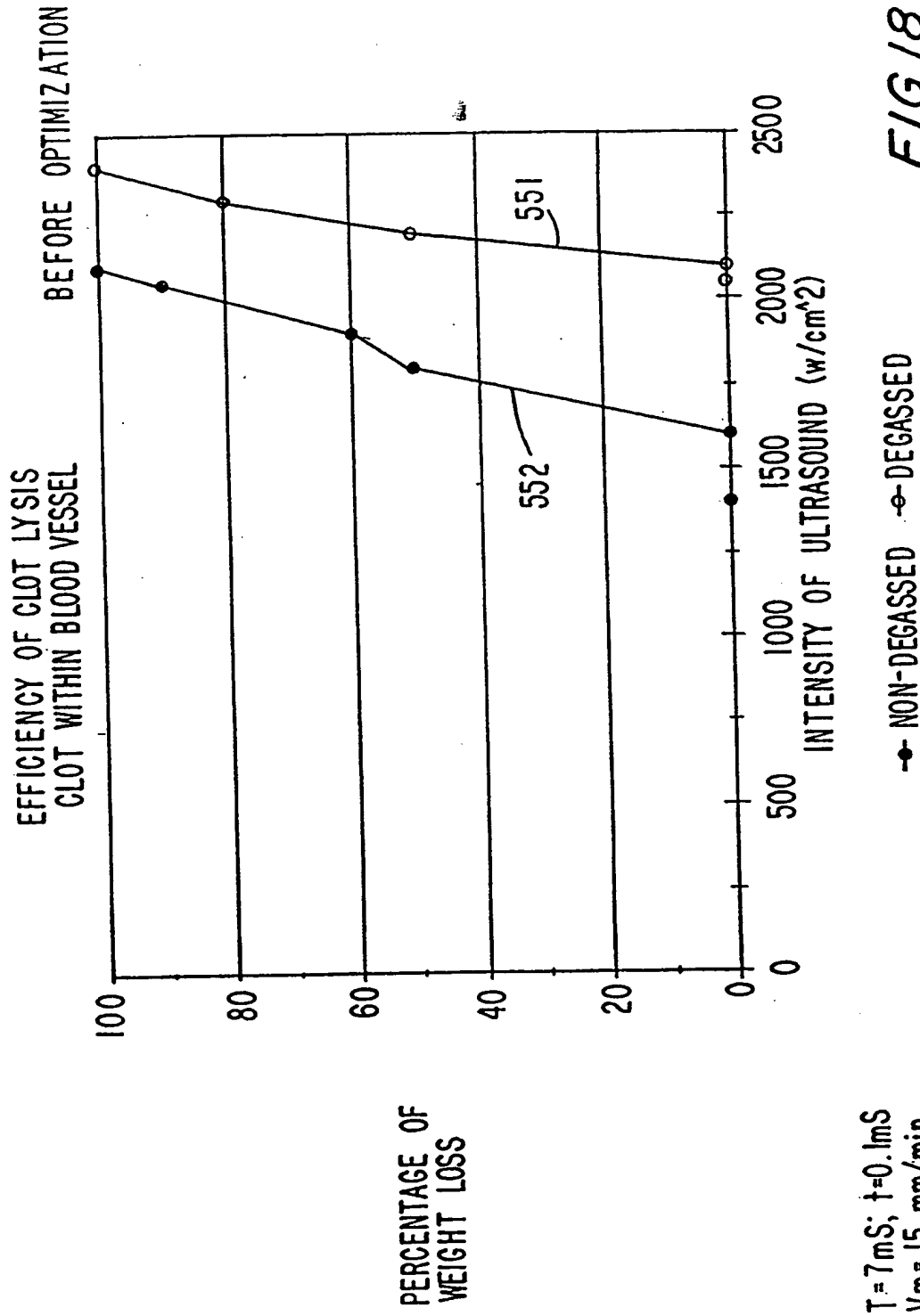
**FIG.16**

19/36

FIG. 17



20/36



SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

FIG. 19A

CLOT WITHIN BLOOD VESSEL

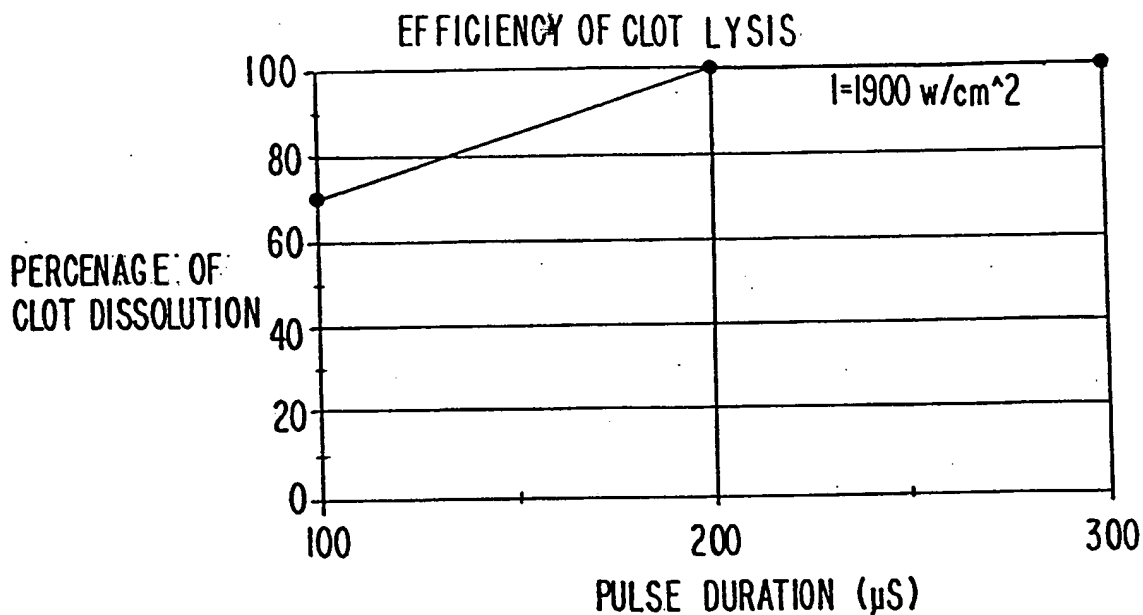
SEARCH FOR OPTIMUM TIME PARAMETER
OF PULSED MODE SONIFICATION

FIG. 19B

CLOT WITHIN BLOOD VESSEL

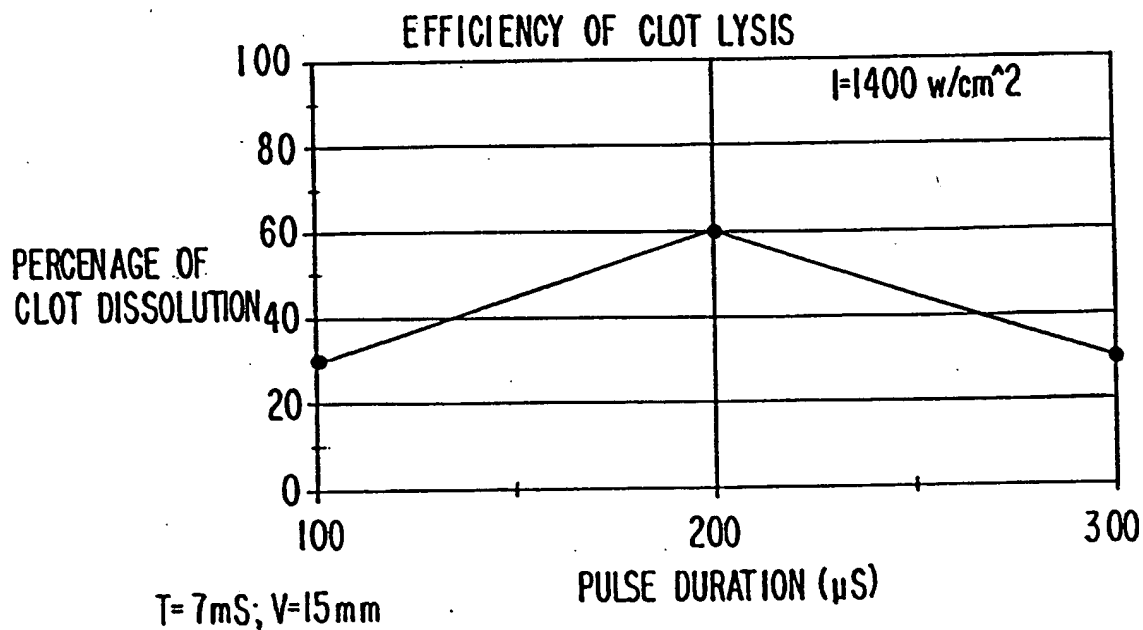


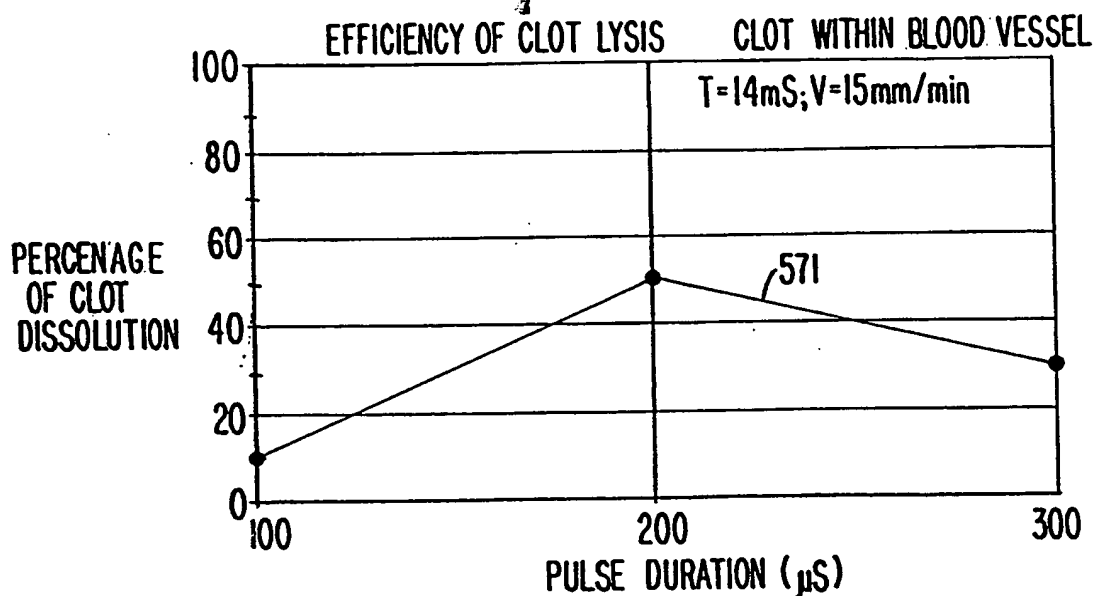
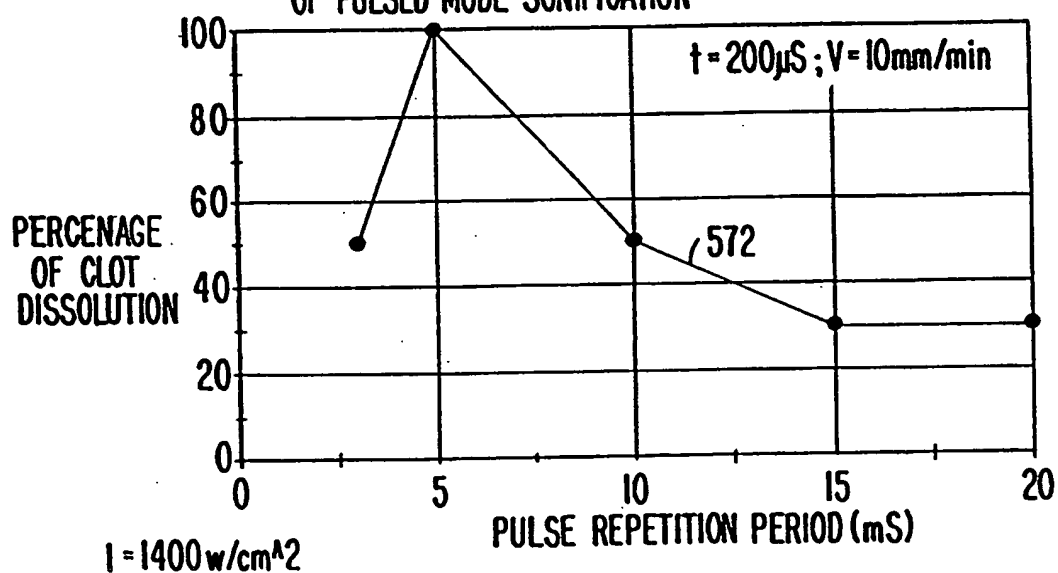
FIG. 20ASEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION**FIG. 20B**SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

FIG.20C SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

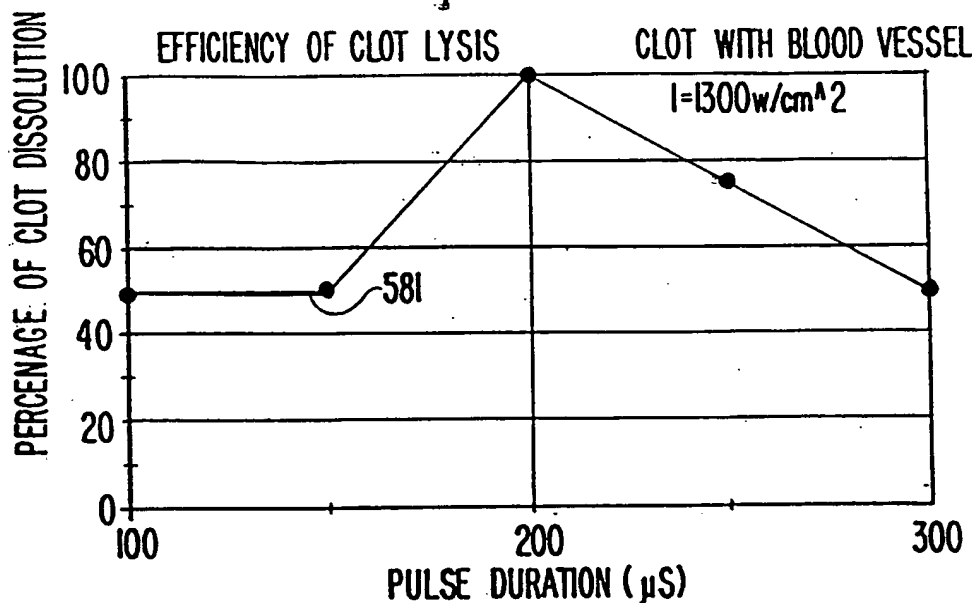
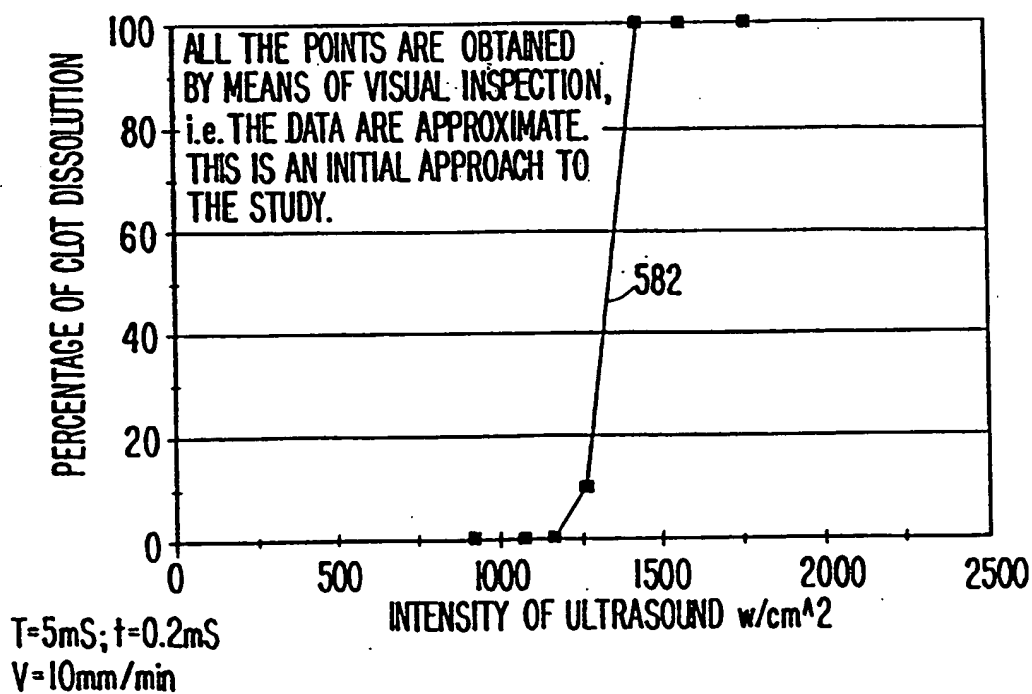
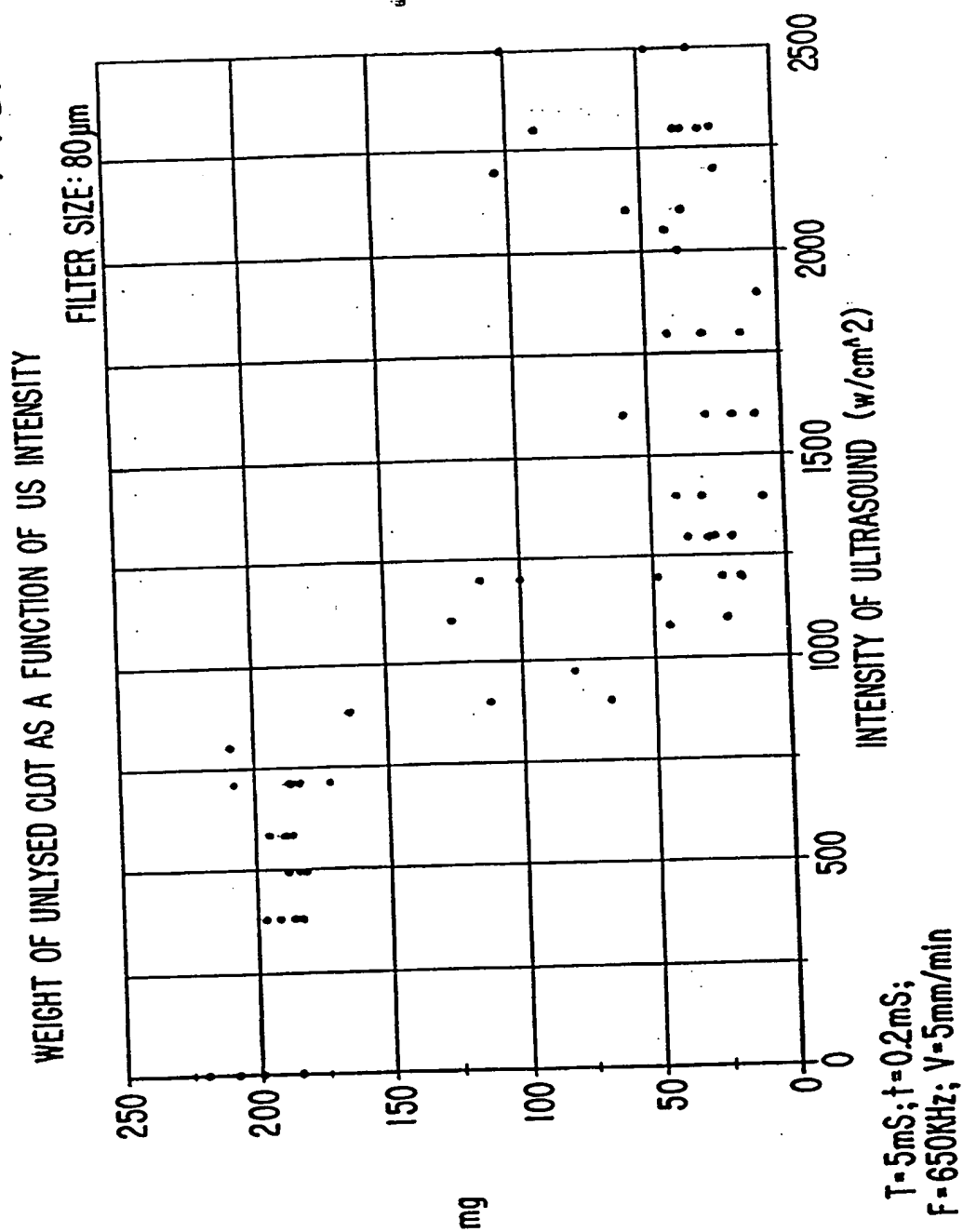


FIG.21 SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION



24/36

FIG. 22



25/36 . .

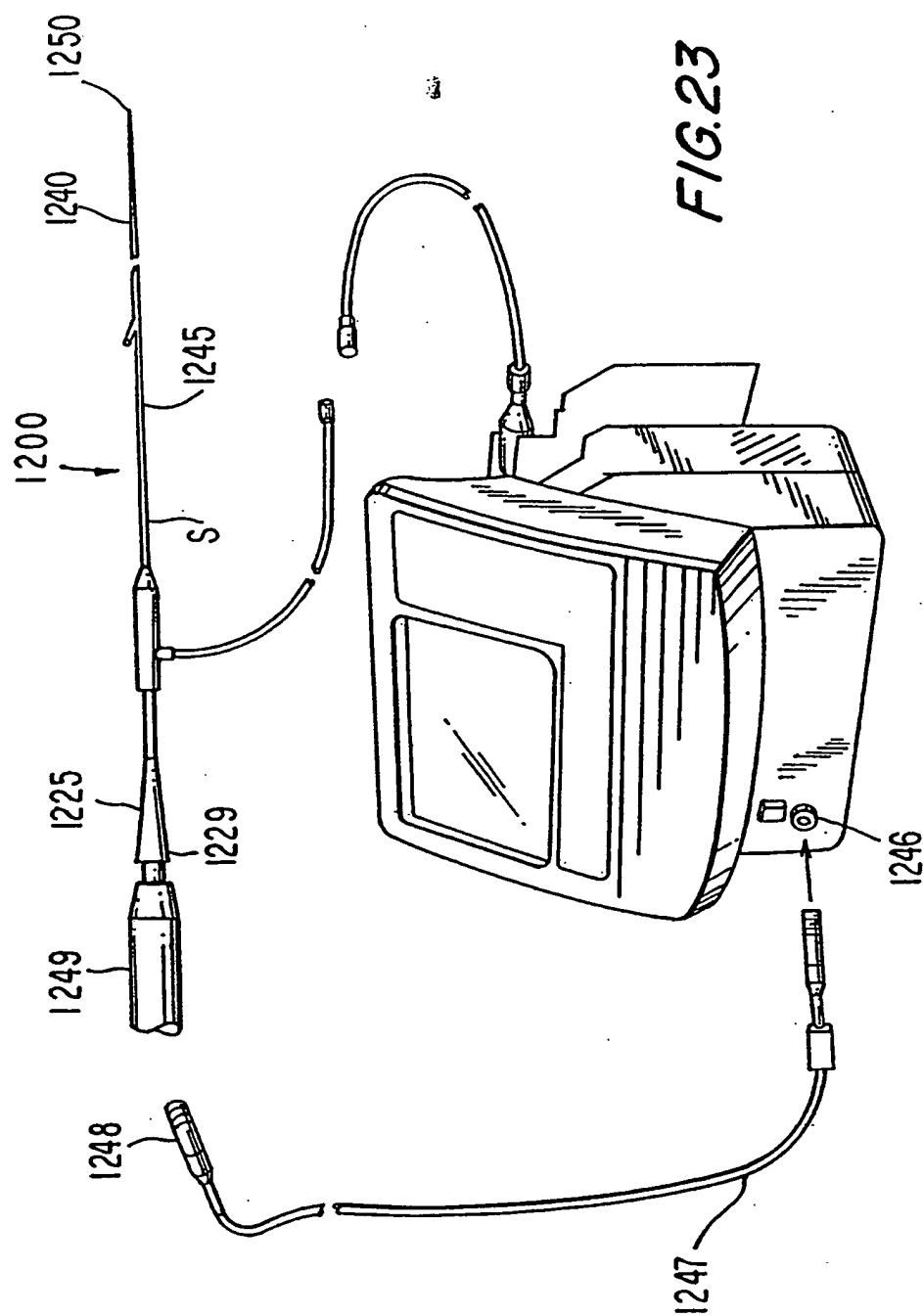
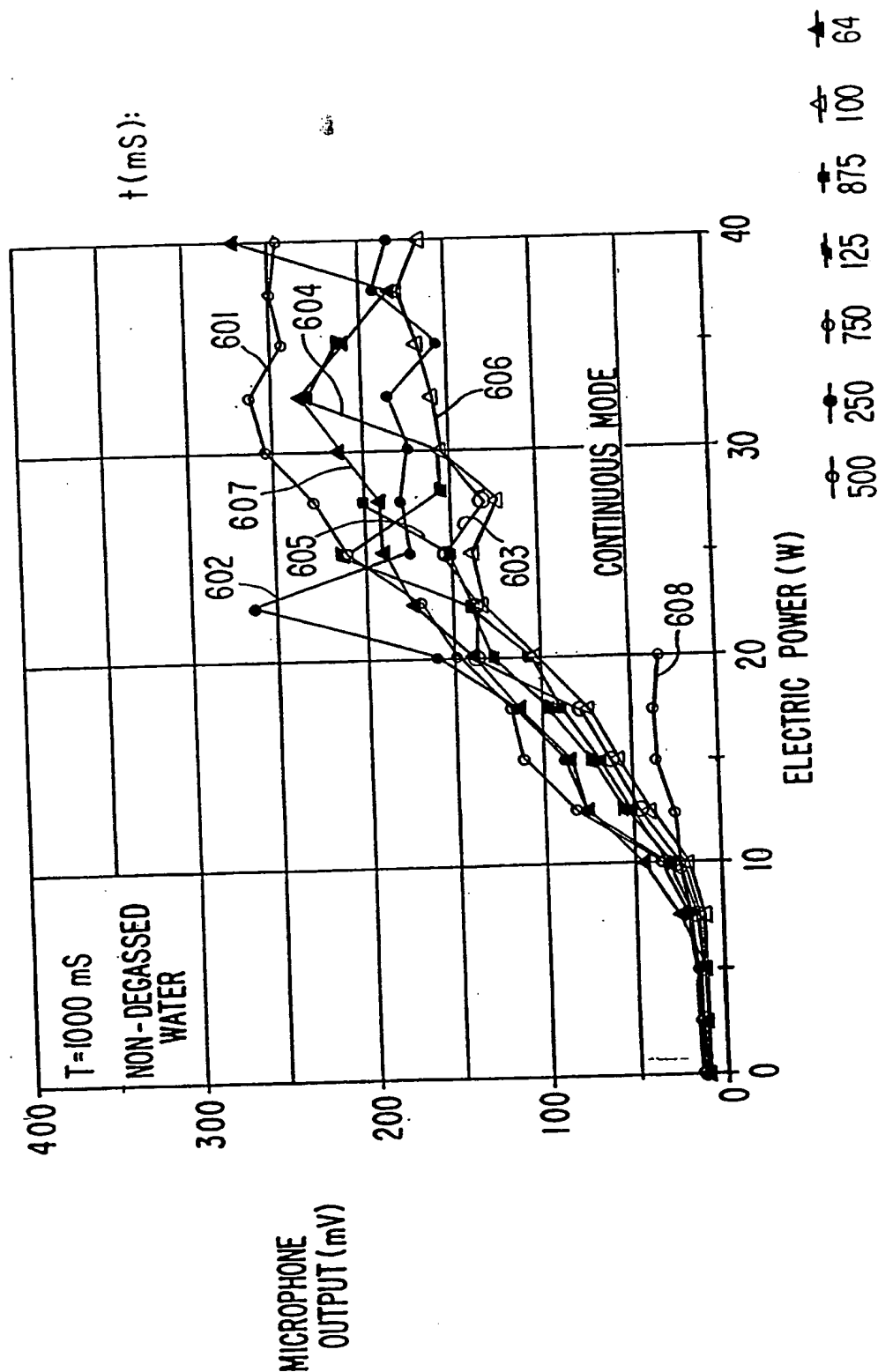


FIG. 24

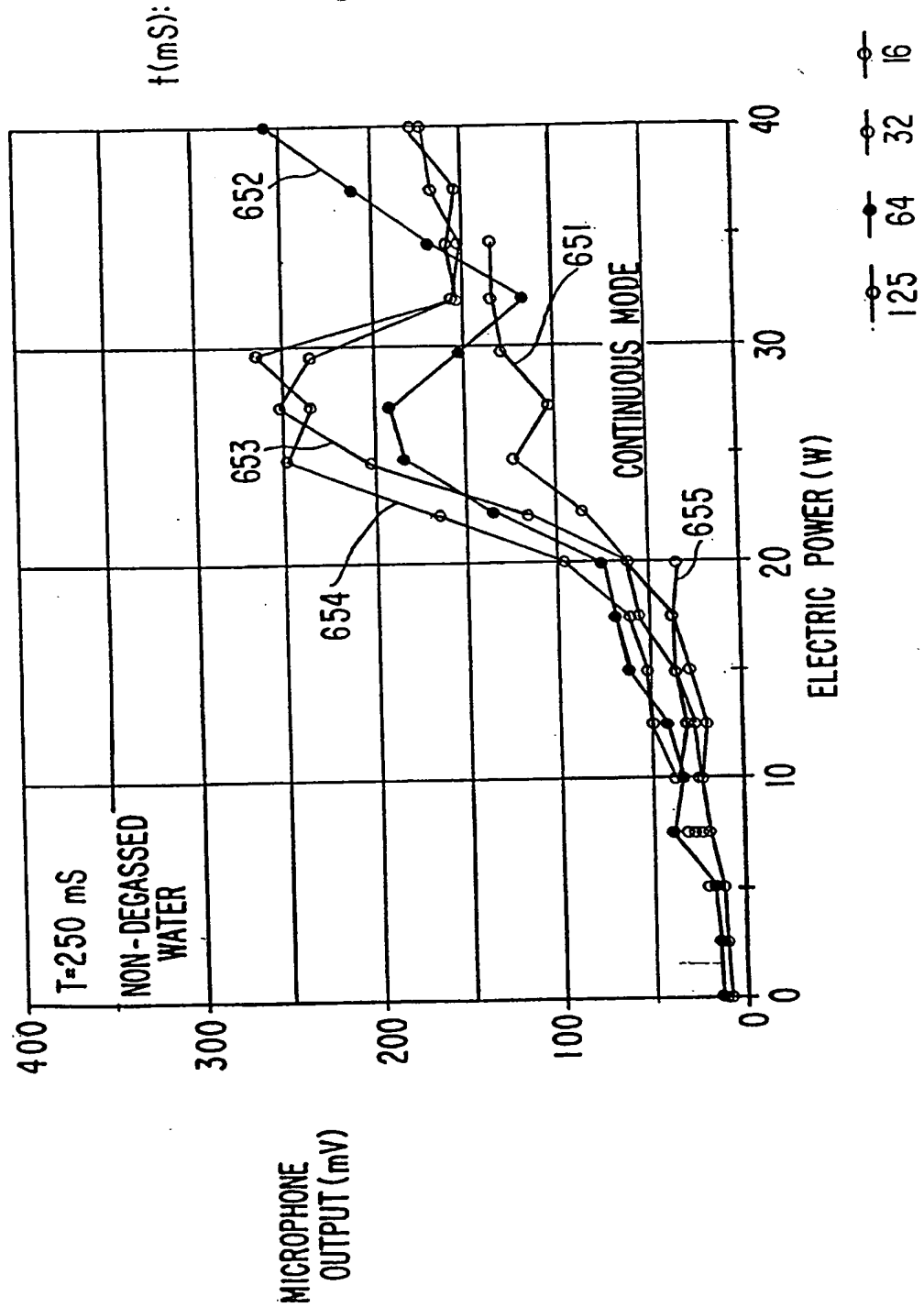
VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER



27/36

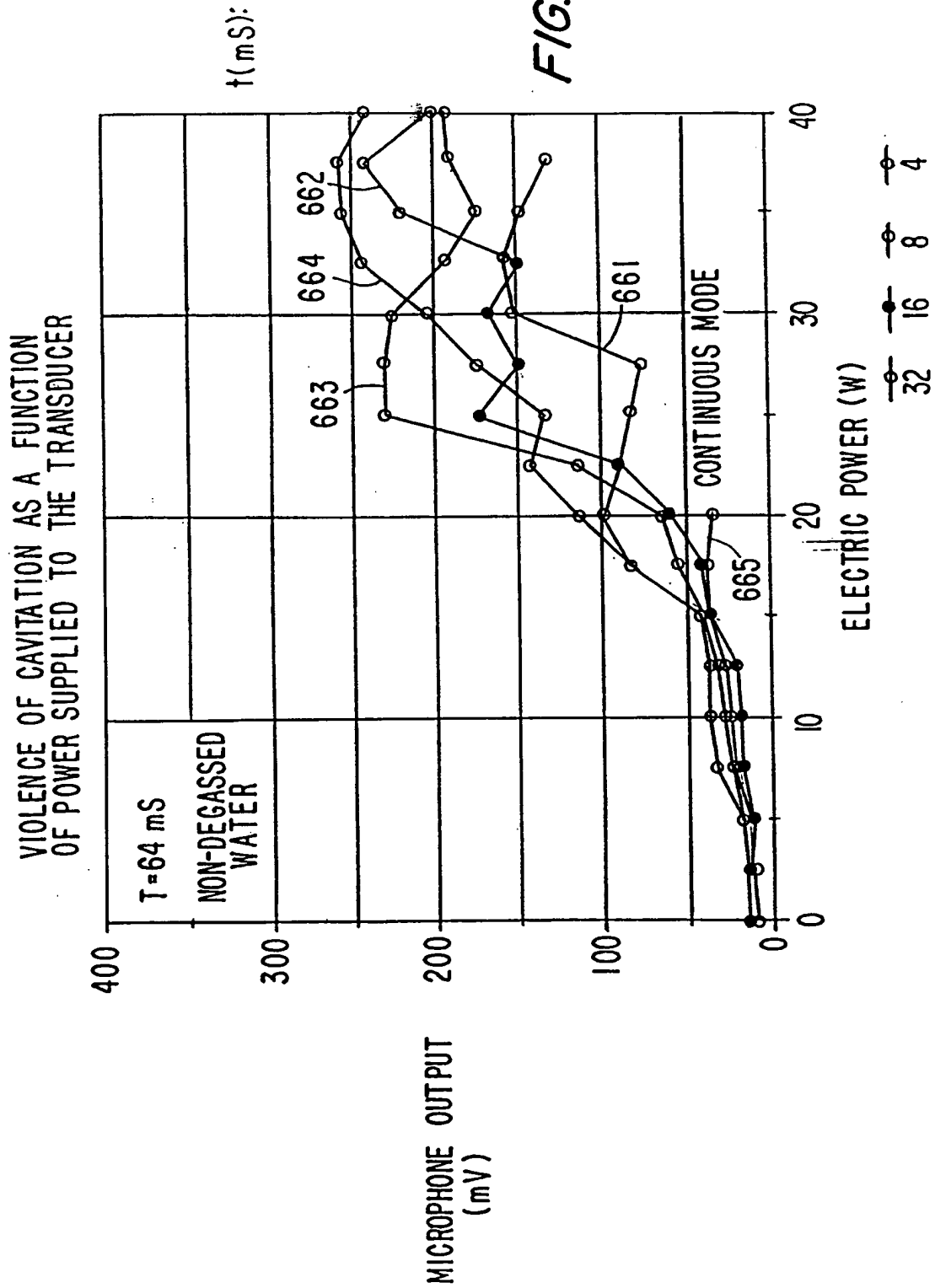
FIG. 25

VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER



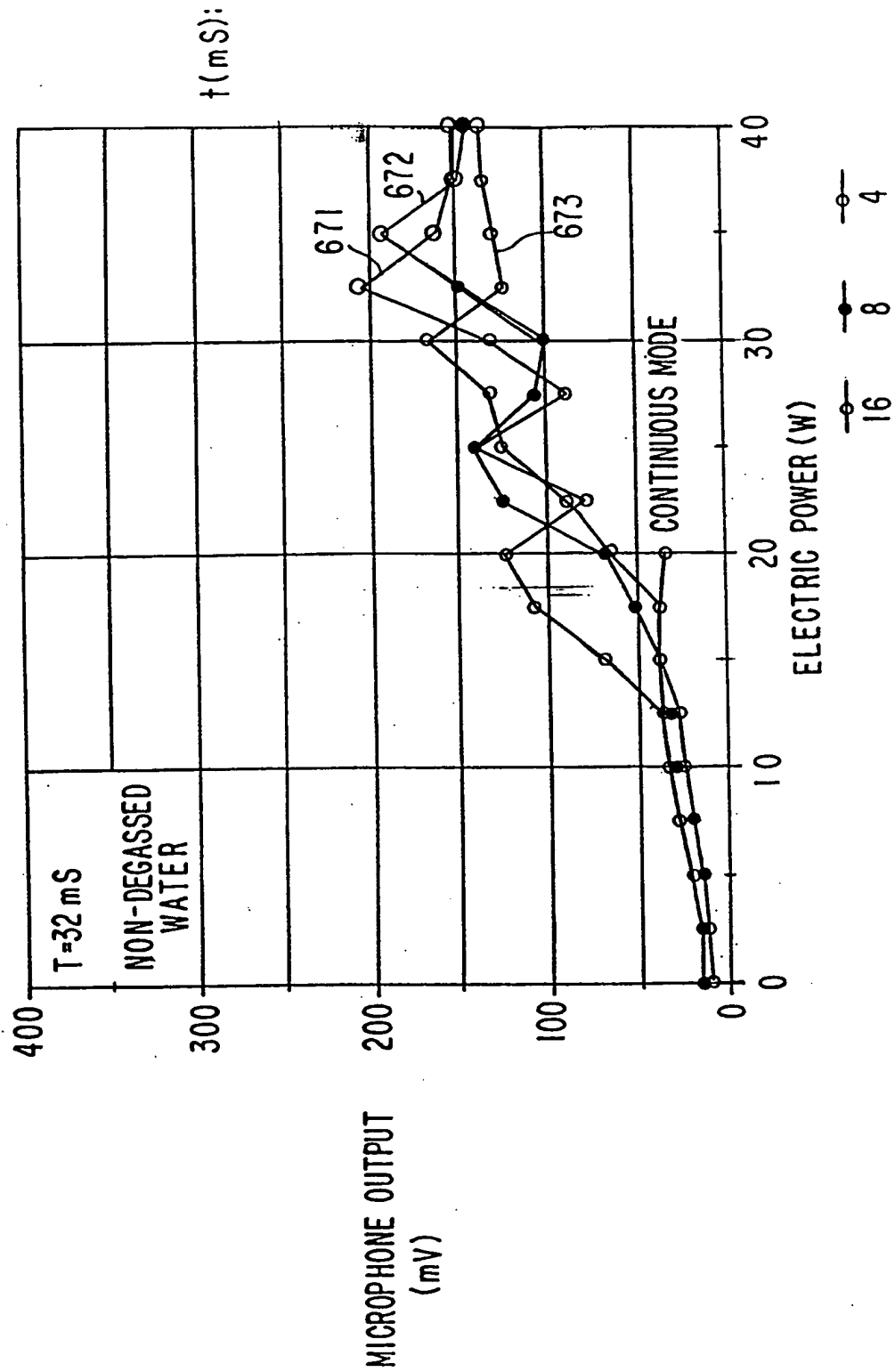
28/36

FIG. 26



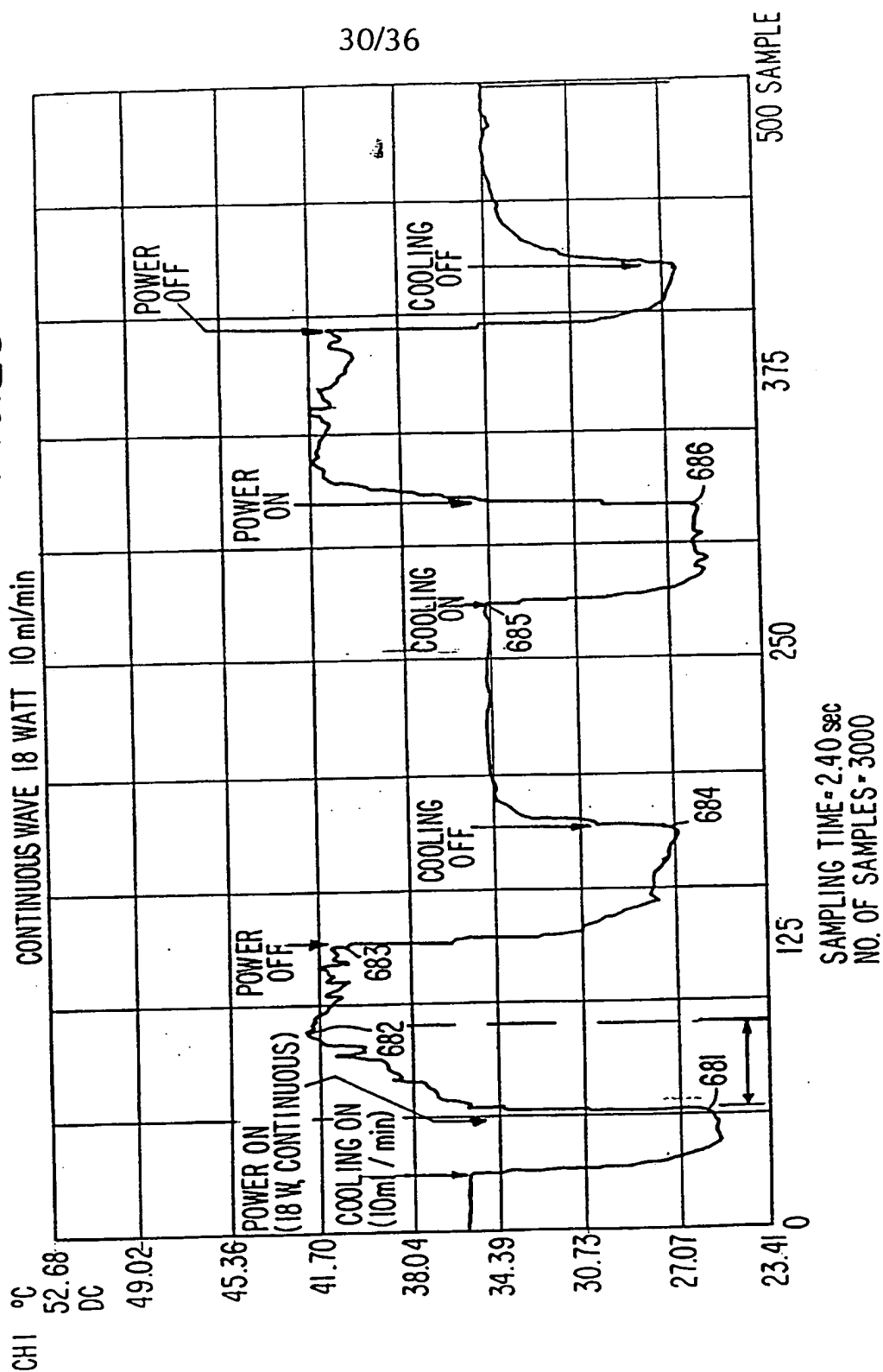
29/36

FIG. 27

VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER

30/36

FIG. 28



31/36

FIG. 29

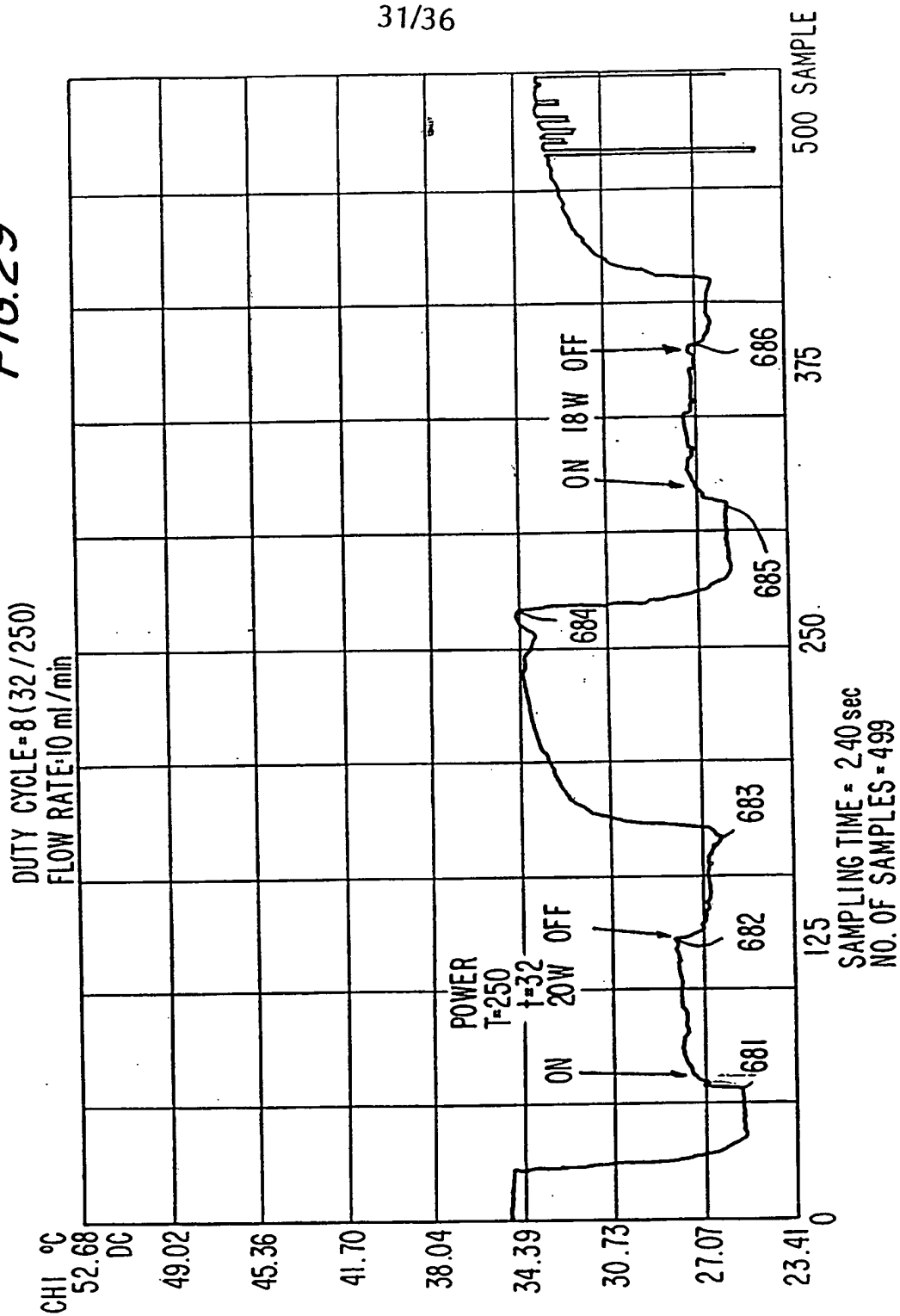
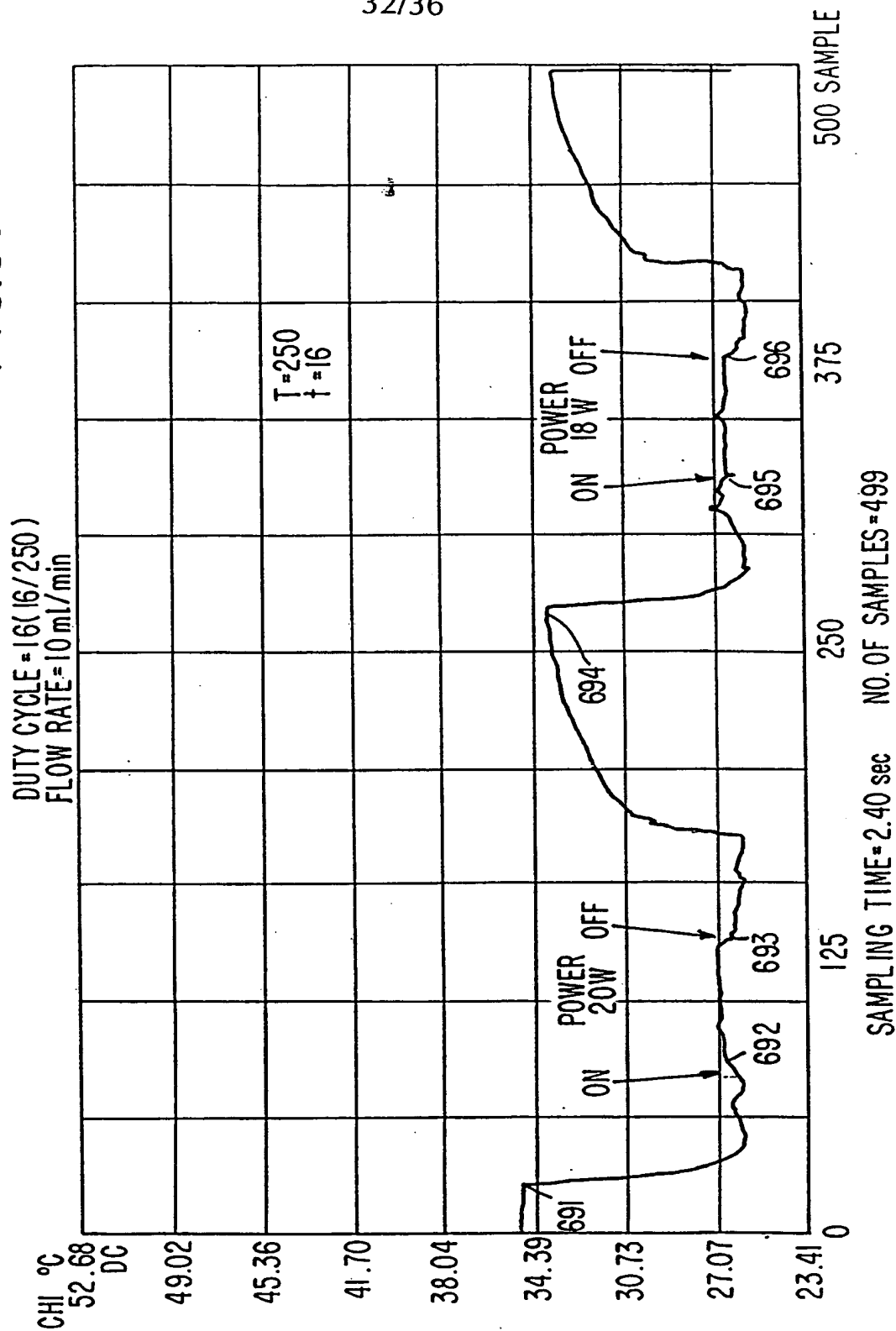


FIG. 30



33/36

FIG. 31

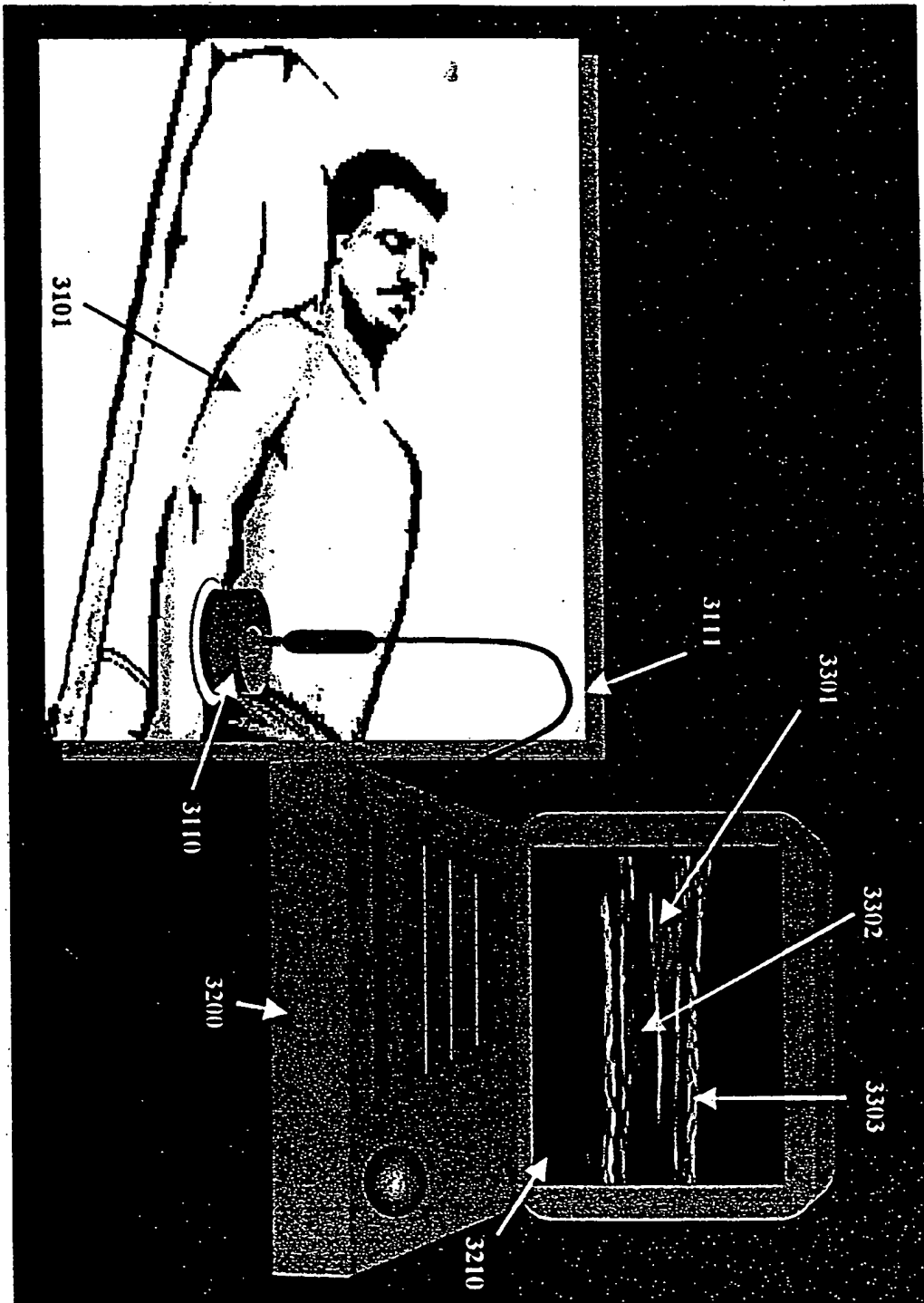
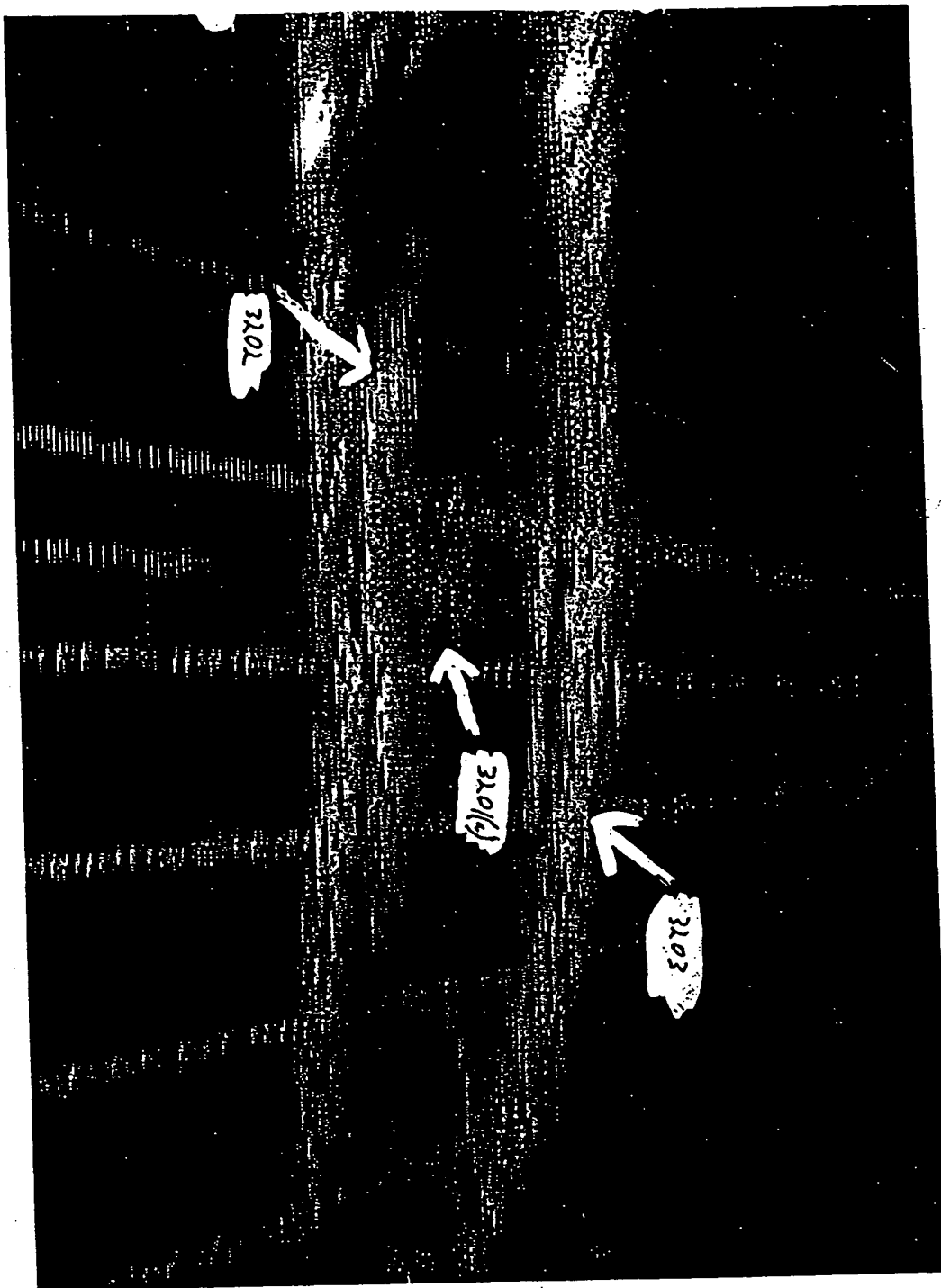


FIG. 3A



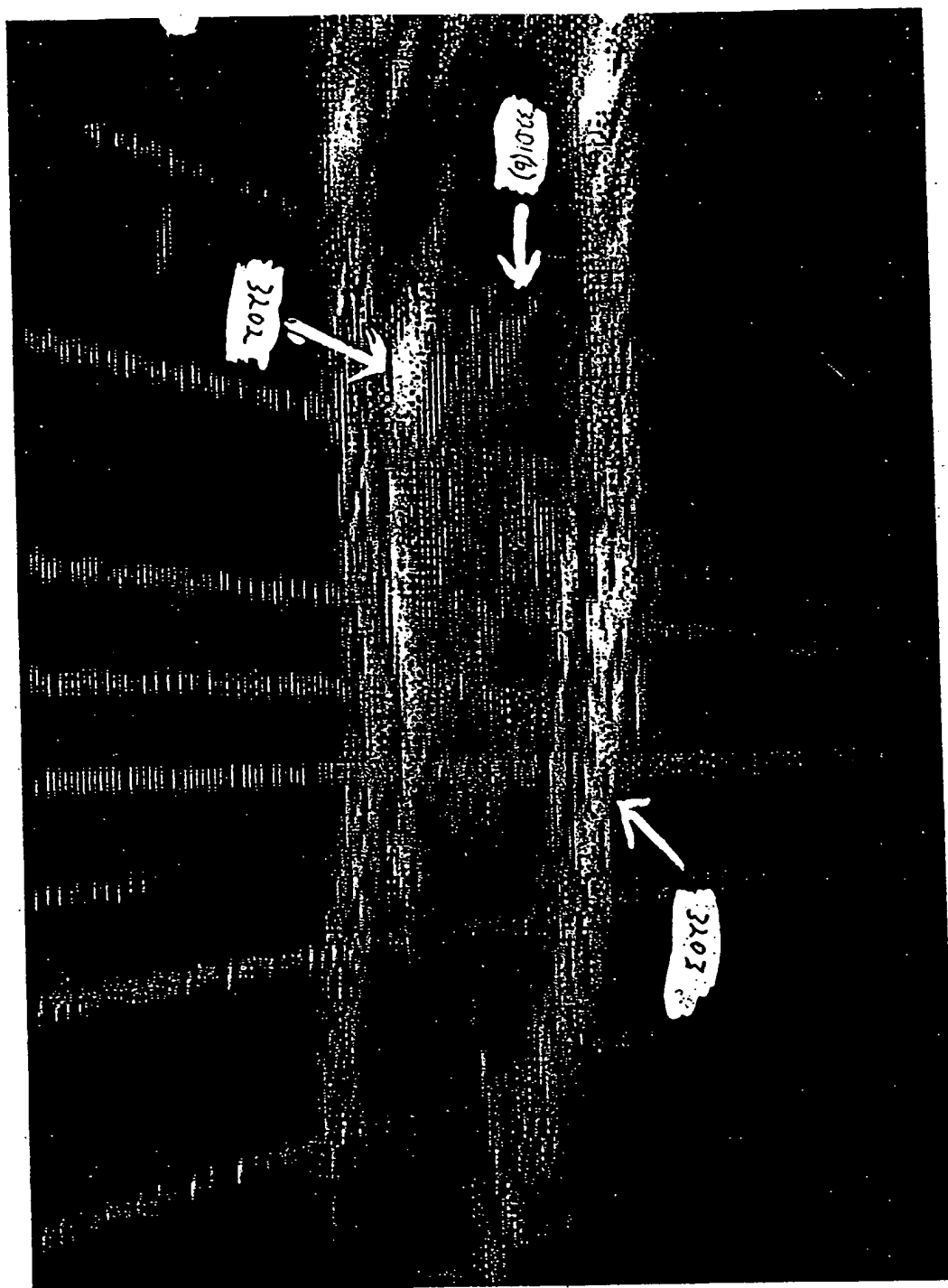


FIG. 328

36/36

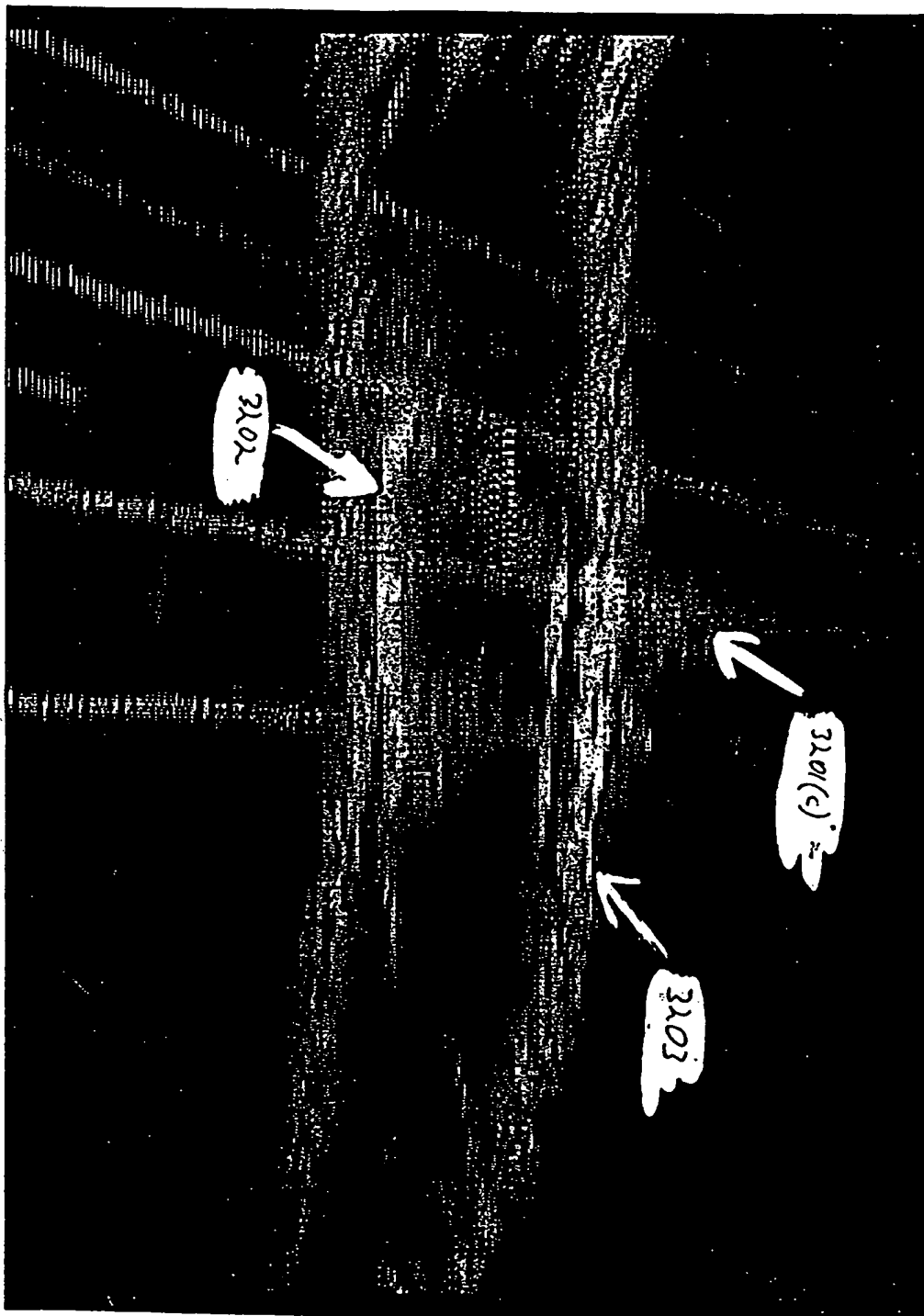


FIG. 32C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/05982

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61N 7/00

US CL :600/439; 601/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 601/2-4 ; 600/439

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,827,204 A (GRANDIA et al.) 27 October 1998, entire document.	1, 3, 5, 7, 8, 10, 13
A	US 5,582,578 A (ZHONG et al.) 10 December 1996, Abstract.	1, 3, 5, 7, 8, 10, 13
A	US 5,601,526 A (CHAPELON et al.) 11 February 1997, entire document.	1, 3, 5, 7, 8, 10, 13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 MAY 2000

Date of mailing of the international search report

13 JUN 2000

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CORRECTED VERSION

**(19) World Intellectual Property Organization
International Bureau**



(43) International Publication Date
14 September 2000 (14.09.2000)

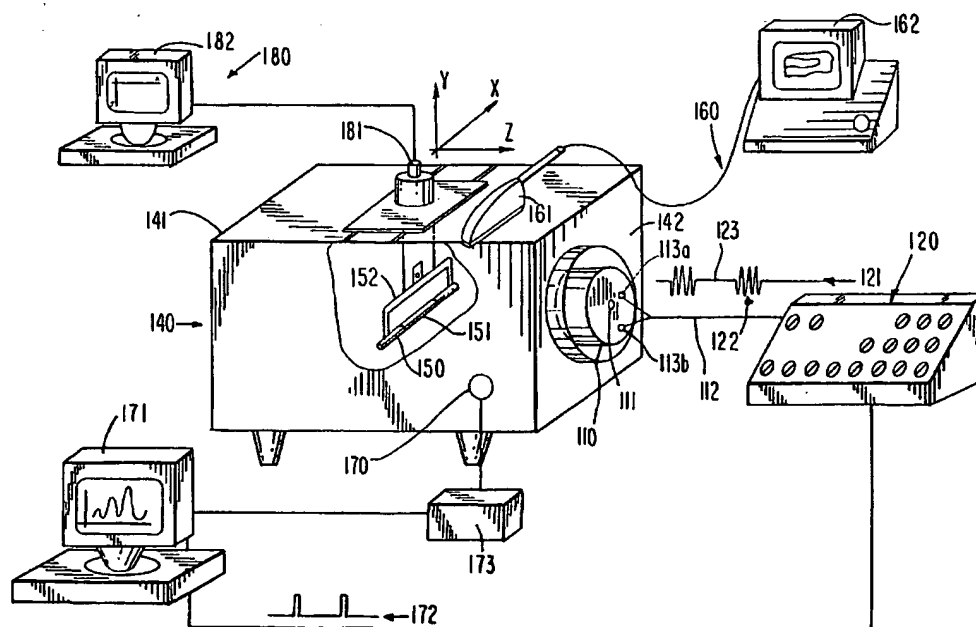
(10) International Publication Number
WO 00/53263 A1

PCT

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|---|--|
| <p>(51) International Patent Classification⁷: A61N 7/00</p> <p>(21) International Application Number: PCT/US00/05982</p> <p>(22) International Filing Date: 8 March 2000 (08.03.2000)</p> <p>(25) Filing Language: English</p> <p>(26) Publication Language: English</p> <p>(30) Priority Data:
 09/264,343 8 March 1999 (08.03.1999) US</p> <p>(71) Applicant: ANGIOSONICS INC. [US/US]; Suite 207,
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 (US).</p> <p>(72) Inventors: ROSENSCHEIN, Uri; 73125 Kefar Daniel
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 FURMAN, Vladimir; Shapira 726/21, Ashkelon (IL).
 KERNER, Efim; Kendler 41/19, Rehovot (IL). FABIAN,
 Izhak; Bar Simantov 4, Yaud (IL).</p> | <p>(54) Agents: ROSENTHAL, Lawrence et al.; Stroock &
 Stroock & Lavan LLP, 180 Maiden Lane, New York, NY
 10038 (US).</p> <p>(81) Designated States (national): BR, CA, JP.</p> <p>(84) Designated States (regional): European patent (AT, BE,
 CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
 NL, PT, SE).</p> <p>Published:
 — <i>with international search report</i></p> <p>(48) Date of publication of this corrected version:
 25 October 2001</p> <p>(15) Information about Correction:
 see PCT Gazette No. 43/2001 of 25 October 2001, Section
 II</p> <p><i>For two-letter codes and other abbreviations, refer to the "Guide-
 ance Notes on Codes and Abbreviations" appearing at the begin-
 ning of each regular issue of the PCT Gazette.</i></p> |
|---|--|

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DUAL TRANSDUCER ULTRASOUND LYSIS METHOD AND APPARATUS



(57) Abstract: An apparatus and method for the application of ultrasound to a location within the body is provided. A cavitation detection system is included so that the effectiveness, and safety of the ultrasound can be monitored during ultrasound treatment. A non-invasive ultrasound system (100) includes a therapeutic focused ultrasound transducer (110).

WO 00/53263 A1

DUAL TRANSDUCER ULTRASOUND LYSIS METHOD AND APPARATUSCROSS REFERENCE TO RELATED APPLICATIONS

5

This is a continuation-in-part of Ser. No. 08/939,289, filed September 29, 1997, the contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

10 The invention relates generally to medical devices and more particularly to a method and apparatus for delivering ultrasound energy to a treatment location within a human or other mammal.

The use of ultrasound devices for ablating, lysing or removing material obstructing blood vessels in humans and to otherwise apply ultrasound to locations within the body for therapeutic purposes has been proposed in the art. One such
15 device for removing material obstructing blood vessels is in the form of an elongated ultrasound transmitting probe. This device includes a cavitation generating tip at the distal end of an elongated transmission member. A transducer is used to convert an electrical signal into longitudinal mechanical vibration, which is transmitted to the tip by the transmission member and causes cavitation within the blood vessel to ablate or
20 lyse the obstruction.

One drawback to such a device is the need to insert and advance the device through a blood vessel to the treatment location. This raises various concerns, such as the opportunity for breakage of apparatus parts within the body, injury to the body from the probe itself and so forth. Another drawback is the need to pump
25 cooling fluid down the length of the device. Examples of such devices are discussed in the following patents, applications and publications, the contents of which are incorporated herein by reference: 5,163,421, issued November 17, 1992; 5,269,297, issued December 14, 1993; 5,324,255; 4,474,180; Ser. No. 08/858,247, filed May 19, 1997 and Julian Frederick, "Ultrasonic Engineering", John Wiley and Sons (1965).
30 However, it is desirable to provide an improved system and method which overcome drawbacks of these conventional devices and methods.

The non-invasive use of ultrasound has also been proposed. For example, U.S. Patent No. 5,524,620 dated June 11, 1996, the contents of which are incorporated herein by reference, describes a non-invasive apparatus and method in which focused acoustic energy is used to ablate a thrombus without the need for
5 invasive devices or drugs. However, non-invasive ultrasound systems can exhibit insufficiently satisfactory results. For example, high power is generally needed to cause adequate lysis. This high power is potentially dangerous and thus, it is desirable to operate a non-invasive system more efficiently, at lower average power, in order to provide a greater margin of safety. The effects of non-invasive ultrasound devices on
10 various locations within the body can also be difficult to predict and control.

Accordingly, it is desirable to provide an improved system and method for the non-invasive application of ultrasound which overcomes inadequacies of the prior art.

SUMMARY OF THE INVENTION

15 Generally speaking, in accordance with the invention, an apparatus and method for the application of ultrasound to a location within the body is provided. The apparatus can advantageously operate at a pulse duration below about 100 milliseconds and in the range 0.1 milliseconds to 100 milliseconds and a pulse repetition period below about 1 second and in the range of 1 millisecond to 1 second.
20 Duty cycle ratios over 5 and preferably over 8 are also advantageous. Therapeutic applications of ultrasound such as for assisting in the treatment of medical conditions such as cancer and/or other ailments are also provided. Treatment can be controlled by monitoring the size and location of the cavitation bubble cloud with an ultrasound imaging device and adjusting parameters such as power or pulse length manually
25 and/or automatically to change the size of the cavitation bubble cloud as desired. Treatment can also be controlled by monitoring the sound given off during cavitation.

Accordingly, it is an object of the invention to provide an improved apparatus and method for treating locations within the body with ultrasound.

A further object of the invention³ is to provide a method and apparatus for determining ultrasound application parameters.

Yet another object of the invention is to provide an apparatus and method for therapeutic applications of ultrasound.

5 Still other objects and advantages of the invention will in part be obvious and will in part be apparent from the specification and drawings.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others, and the apparatus embodying features of construction, combinations of elements and arrangements of
10 parts which are adapted to effect such steps, all as exemplified in the following detailed disclosure, and the scope of the invention will be indicated in the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the invention, reference is had to the following description taken in connection with the accompanying drawings, in which:

15 FIG. 1A is a schematic perspective view of a system for the non-invasive use and testing of ultrasound energy;

FIG. 1B and 1C are front and side views of the transducer shown in FIG 1A;

20 FIG. 2 is a graph showing hydrophone output, in decibels, as a function of transversal displacement of the hydrophone along the Y axis to establish the focal width of ultrasound in the Y direction;

FIG. 3 is a graph showing hydrophone output voltage as a function of transducer input voltage, showing that electric potential above 160 volts, and therefore increased wattage, caused a decrease in hydrophone output as a result of exceeding the
25 cavitation threshold of the medium;

FIG. 4 is a graph showing hydrophone output voltage as a function of displacement of the transducer along the Z-axis for both short duration pulses and relatively longer duration pulses, showing that a longer pulse duration (τ) can initiate cavitation;

FIG. 5 is a graph showing hydrophone output voltage as a function of Z-axis displacement for various pulse durations, showing that longer pulse durations were associated with larger decreases in acoustic amplitude after exceeding the cavitation threshold;

5 FIG. 6 is a graph showing hydrophone output voltage as a function of Z-axis displacement for transducer inputs of varying voltage, showing that cavitation was evidenced by a decrease in actual hydrophone output from the theoretical output;

 FIG. 7 is a graph showing change in percentage of clot mass dissolution as a function of change in the pulse repetition period (T), showing that an appropriate
10 pulse repetition period has a significant effect on the efficiency of clot lysis;

 FIG. 8 is a graph showing percentage of clot mass dissolution as a function of pulse duration (τ), showing a strong dependency of clot dissolution and danger to the blood vessel on pulse duration;

 FIG. 9 is a graph showing rate of clot mass dissolution as a function of
15 intensity at the focal area;

 FIGS. 10A and 10B are ultrasound images of a clot within an artery segment, before and after ultrasound treatment;

 FIGS. 11 and 12 are graphs showing microphone output voltage as a function of ultrasound peak intensity in a buffer solution and in a clot, showing that
20 ultrasound initiated randomly, but that once initiated, it could be maintained at decreased intensities and that the threshold and slope are different for the buffer and clot;

 FIGS. 13 and 14 are graphs showing microphone output as a function of ultrasound intensity, when blood is acted upon by ultrasound of different pulse
25 repetition periods (T), showing that shorter T 's correlate to lower intensity thresholds and ultimately lower cavitation intensity;

 FIGS. 15 and 16 are graphs showing the influence of pulse duration on cavitation activity of a buffer solution and blood, respectively;

FIG. 17 is a graph showing microphone output, which is related to cavitation activity, as a function of pulse duration in both a blood and a buffer solution;

FIG. 18 is a graph showing percentage of weight loss of a clot as a function of ultrasound intensity for a non-degassed and degassed sample, showing a lower intensity threshold and lower intensity requirement for the non-degassed system;

FIGS. 19A and 19B are two graphs showing percentage of clot dissolution as a function of pulse duration at two different power settings, at $T = 7$ ms, showing increased clot dissolution with increased intensity and that optimal pulse durations exist for certain other parameters;

FIGS. 20A, 20B and 20C are three graphs showing percentage of clot dissolution as a function of pulse duration (τ), pulse repetition period (T), and pulse duration (τ), respectively, at intensities of 1400 W/cm^2 , 1400 W/cm^2 and 1300 W/cm^2 respectively and shows that optimal parameters can be intensity independent;

FIG. 21 is a graph showing percentage of clot dissolution as a function of ultrasound intensity, manifesting threshold for clot lysis;

FIG. 22 is a graph showing the weight of unlysed clot as a function of ultrasound intensity, manifesting a threshold for clot lysis;

FIG. 23 is a perspective view of an invasive type ultrasound transmission system, constructed in accordance with an embodiment of the invention;

FIGS. 24-27 are graphs showing cavitation activity as a function of transducer power, showing the difference between continuous and pulsed activation;

FIGS. 28-30 show ultrasound probe temperature in activated and unactivated states, both with and without the use of cooling fluid, in a continuous wave mode of probe operation, and in duty cycles of 8;

FIG. 31 shows a non-invasive ultrasound treatment system with a combined ultrasound imaging and ultrasound treatment transducer and a display screen permitting an operator to monitor the treatment; and

FIGS. 32A, 32B and 32C show that adjusting pulse duration can affect the size of the cavitation bubble cloud within a vessel.

DESCRIPTION OF PREFERRED EMBODIMENTS

Significant therapeutic effects can be achieved by applying ultrasound to locations within a living body. Generally, a transducer converts an electrical signal to mechanical vibration, which causes the propagation of ultrasound waves through some medium or media. If these waves are of sufficient intensity, they create cavitation within a medium at a desired location as micro bubbles are formed and collapse. This generates extraordinarily high activity at the cavitation site.

A transducer can be operated in a continuous mode or in a pulsed mode. In a continuous mode, the signal to the transducer is always causing the transducer to generate sufficient vibration to maintain cavitation at the desired location. In a "pulse" mode, the signal amplitude is reduced sufficiently (or eliminated) to permit cavitation to pause between pulses of high amplitude during which cavitation occurs. Certain conventional pulsing methods apply ultrasound in one to several second doses, followed by pauses of approximately equal duration or even durations longer than the duration of the activating signal. This is conventionally performed to permit objects which became hot during the activation process to cool down. It has been discovered that applying ultrasound in an improved pulsed mode can provide substantial advantages, compared to conventional pulsing modes of operation.

Referring to FIG. 1A, an example of a system for providing the non-invasive application of ultrasound to a test sample in a model representing a body part, which can be readily modified to apply ultrasound to a location within a living body, is shown generally as non-invasive ultrasound application system 100. Non-invasive ultrasound system 100 includes a therapeutic focused ultrasound transducer 110, which is activated by an electrical signal from a signal generator 120. Therapeutic transducer 110 can be constructed to operate at up to 750 KHz and can be formed with a 1-3 ceramic composite. A 1-3 composite transducer includes rods of PZT inserted into a polymer support and has very high energy transfer efficiency. Front and side views of one embodiment of transducer 110 are shown in FIGS. 1B and 1C. Therapeutic transducer 110 includes a hole 111 at the center thereof. Hole 111

permits the use of an optional ultrasound imaging probe (not shown) which can guide and monitor the therapy with ultrasound during application. One example of a suitable transducer, which was used in experiments presented herein, is about 45 mm thick, has an overall radius of 46 mm, a central active area with a radius of 40 mm and a central bore with a radius of about 10 mm. Electrical connections are on either side of the central bore at disk shaped depressions having an 8 mm radius. Alternative transducers can be substituted.

To operate transducer 110, generator 120 sends a signal 121 through a pair of electric wires 112, which are coupled to transducer 110 at attachment points 113a and 113b. Signal 121 is formed with a plurality of energy pulses 122 of duration τ at an amplitude (A) and a frequency (f). As used herein, a pulse will be considered the "on" portion 122 of signal 121, which is of sufficient amplitude to maintain cavitation and is followed by an "off" section 123 of signal 121 of insufficient amplitude to maintain cavitation. The duration of time between the beginning of successive pulses 122 is referred to as pulse repetition period T. It has been determined that pulse duration τ is advantageously significantly smaller than pulse repetition period T.

To model the effects ultrasound emitted from therapeutic transducer 110 would have on a location within a living body, a model system 140 was constructed. Model system 140 includes an open Plexiglas water tank 141 with a hole in a front side 142 for inserting therapeutic transducer 110. Tank 141 was filled with water, which was either degassed or non-degassed, depending on the particular experiment to be run. When water was not degassed, it included small air bubbles which served as a nuclei for cavitation initiation. Decreasing the number of bubbles in the water increases the energy needed to initiate cavitation.

To obtain information about the focal region of ultrasound emitted from transducer 110, a hydrophone (not shown) was positioned at various locations within a dedicated tank. It was found that when activated by generator 120 at low intensities below the cavitation threshold, transducer 110 creates an acoustic field with a focal region having an elongated ellipsoid or cigar shape.

To obtain information regarding the effects of ultrasound on clots within a living body, a bovine vessel 150 having a clot 151 therein or a clot attached to the front of a bovine vessel wall was suspended within tank 141 by a specimen holder 152. Depending on the experiment to be run, vessel 150 was filled with either blood or a buffer solution. The vessel 150 and the clot 151 were moved by a computerized x-y positioning a system 180 through a mounting 181 and a computer controller 182. Certain information regarding the effects of applied ultrasound were compiled with an ultrasound imaging device 160, formed with an imaging ultrasound transducer 161, coupled to a processor 162 for interpreting information received from transducer 161 and displaying an image thereof. Additional information was compiled through the use of a microphone 170 attached to tank 141, coupled to a frequency analyzer 171 through an amplifier 173, which also receives a trigger signal 172 from generator 120. Trigger signal 172 corresponds to transducer activation signal 121, so that only sound transmitted from microphone 170 when transducer 110 is activated will be analyzed.

It was determined that advantageous benefits can be achieved when ultrasound is applied at a pulse duration τ not greater than about 100 milliseconds (msec). A range of about 0.01 to 100 milliseconds is preferred. Also, pulse repetition periods T below about 1 second are preferred, as are pulse repetition periods in the range 1 millisecond to 1 second. Duty ratios $T/\tau \geq$ about 5, and preferably ≤ 8 are preferred.

Non-invasive therapeutic ultrasound can be practiced at a frequency of about 100 to 1000 KHz and far broader. Invasive-type (probe-based) therapeutic ultrasound can be practiced at a frequency range of 20 to 100 KHz and far broader. At a frequency of preferably 100 to 1000 KHz advantageous operating parameter include $T =$ about 1 to 100 milliseconds, preferably about 2.5 to 90 milliseconds and more preferably 2.5 to 75 milliseconds and/or $\tau =$ 0.01 to 2.0 milliseconds, preferably 0.02 to 1.1 milliseconds and more preferably 0.1 to 0.3 milliseconds. These parameters are particularly well suited for a non-invasive-type device, particularly one applying ultrasound at $I \geq$ about 750 W/cm², more preferably \geq about 1000 W/cm².

At a frequency range preferably of 20 to 100 KHz, advantageous operating parameters include $T \leq$ about 1000 milliseconds preferably \leq about 600 milliseconds, more preferably about 100 to 500 milliseconds and/or $\tau \leq$ about 100 milliseconds, preferably about 10 to 100 milliseconds, more preferably 20 to 60
5 milliseconds. These parameters are particularly well suited for use with an invasive-type device, especially one operated at a peak power output of over 10 watts, such as one operated at 10-40 watts, preferably 15-30 watts. When pulse parameters are correctly selected, an invasive-type probe can be operated with substantially no cooling fluid.

10 Substantial benefits can be achieved by monitoring the progress of ultrasound treatment. This can be accomplished in at least two ways. In one embodiment of the invention, a microphone is placed on the body and cavitation can be detected by its audible signal. This can enable an operator to decrease power and/or change the pulse parameters until an acceptable audible signal is detected.
15 Thus, by establishing a set of standardized acoustic signals produced by cavitation from a therapeutic ultrasound treatment, standardization in treatment can be improved. Furthermore, systems can be established which automatically reduce power or change pulse parameters if too high a cavitation signal is detected and automatically increase power or change pulse parameters if too low a signal is detected.

20 In another embodiment of the invention, a conventional ultrasound imaging transducer is used in conjunction with therapeutic ultrasound. An operator can observe not only a clot being broken up, for example, but the size and location of the cavitation cloud caused by the ultrasound. Thus, an operator can increase or decrease the power as needed, as described above. An operator can also pinpoint the
25 location of the cavitation. Furthermore, it has been found that changing the pulse duration can change the size of the cavitation cloud. Accordingly, an operator can increase pulse duration in order to increase the size of the cavitation cloud or decrease the pulse duration to decrease the size of the cavitation cloud in order to insure a cloud of appropriate volume. Thus, if desired, the size of the cavitation cloud can be

increased to match the size of a clot and decreased if cavitation is occurring in an unneeded location.

In still another embodiment of the invention, computer recognition or other automated systems can detect the presence of cavitation, based on the signal received from the imaging transducer. This information can be used to automatically adjust parameters to optimize cavitation. Alternatively, this information can be used to display a cavitation level to a user or to sound a warning or even shut down the system if too much or too little (or none) cavitation is being produced.

In a preferred embodiment of the invention, the two transducers are concentric. The imaging transducer is preferably able to be rotated on the symmetry axis to give a long view, along the length of the vessel, which will appear as two parallel lines and a short axis, through the length of the vessel, which will appear as a ring.

The location of the clot can be determined through the ultrasound imaging transducer. To aim the transducer, it is positioned such that the vessel is parallel to one of the X-Y axis of the transducer movement system.

Referring to FIG. 31, a patient 3101 is seen receiving an ultrasound treatment via a transducer unit 3110. Unit 3110 contains an ultrasound imaging transducer concentric with an ultrasound generating transducer. Transducer unit 3110 is coupled via line 3111 to a control unit 3200, which is coupled to a display screen 3210. Display screen 3210 displays the image from the display transducer. By monitoring display screen 3210, an operator can determine the size and location of a cavitation cloud 3301 with respect to a clot 3302 in a vessel 3303. Thus, the size and location of cavitation 3301 can be matched to clot 3302 and to vessel 3303.

The following examples illustrating the non-invasive application of ultrasound were conducted in a water tank with a system having the general construction shown in FIG. 1A. These examples are provided for purpose of illustration only, and are not intended to be construed in a limiting sense.

Example 1

The transducer was operated at a frequency of 750 KHz, at a pulse duration of $\tau = 20 \mu\text{s}$, a pulse repetition period of $T = 74 \text{ ms}$ and a potential of 46 V. The hydrophone output was measured in decibels as a function of transversal displacement in mm along the Y axis, parallel to the transducer plane and corresponded to the predicted cigar shape at a distance of 5 cm from the transducer. The results are shown in FIG. 2.

Example 2

The hydrophone response at the focal point both above and below the cavitation threshold was measured. Referring to FIG. 3, it can be seen that when $\tau = 20 \mu\text{s}$ and $T = 74 \text{ ms}$ and transducer input was increased above about 160 volts, the effects of cavitation can be determined by a decrease in hydrophone response at the focal point, as energy is absorbed before the focal point, leading to a decrease of sound energy at the focal point itself.

Example 3

The effects of pulse duration on cavitation were measured by operating the transducer at an input potential of 180 V, $T = 75 \text{ ms}$ and measuring hydrophone output in a water filled tank at $\tau = 1100 \mu\text{s}$ (curve 51 in FIG. 4) and $20 \mu\text{s}$ (curve 52 in FIG. 4). As shown in FIG. 4, the longer pulse duration led to cavitation, whereas the shorter pulse duration exhibited no breakdown in focal depth. Accordingly, the initiation of cavitation depends not only on input voltage as has been believed, but also on pulse duration.

Example 4

The effects of pulse duration on cavitation were also analyzed for seven different pulse durations at 190 V and $T = 11 \text{ ms}$. Referring to FIG. 5, curve 61 is from a duration of $20 \mu\text{s}$, curve 62 is from a duration of $40 \mu\text{s}$, curve 63 is from a duration of $60 \mu\text{s}$, curve 64 is from a duration of $80 \mu\text{s}$, curve 65 is from a duration of $100 \mu\text{s}$, curve 66 is from a duration of $150 \mu\text{s}$ and curve 67 is from a duration of $200 \mu\text{s}$. Longer pulse durations were shown to be directly proportional to larger decreases in hydrophone output and consequentially, increased cavitation activity.

Example 5

The effects of increased voltage (increased power and intensity) on cavitation were analyzed more fully, by measuring hydrophone output as a function of Z-axis displacement at $T = 200$ ms and $\tau = 20$ μ s, at various input voltages. Referring to FIG. 6, curve 80 shows a theoretical plot at 190 volts, if no cavitation had occurred, curve 81 is from 100 volts, curve 82 is from 142 volts, curve 83 is from 155 volts and curve 84 is from 190 volts. Higher electrical input corresponded to higher amplitude and larger decreases in acoustic amplitude, compared to a theoretical prediction and hence, greater cavitation effect.

10 Example 6

The apparatus shown in FIG. 1A was used to dissolve a blood clot attached to the front of a wall taken from a bovine blood vessel. Referring to FIG. 7, the transducer was operated at a duty cycle $(T/\tau) = 8$ and an intensity of 1300 W/cm² and the pulse repetition period was varied over a range of about 0.5 to 27 ms. Optimal results were achieved in a range of about $T = 4$ to 10 ms, with peak clot dissolution efficiency at a pulse repetition period of about 8 ms and a pulse duration of about $\tau = 1$ ms. Thus, the operating parameters including a duty cycle of about 8 were deemed acceptable.

Example 7

20 The use of non-invasive ultrasound to lyse a clot attached to a vessel wall at parameters of $I = 1300$ W/cm² and $T = 8$ ms, for pulse durations ranging from about 0.07 ms to about 5 ms were performed and the results are presented in FIG. 8. The results show optimal clot dissolution at pulse durations of about $\tau = 0.5$ to 1.0 ms. It was also determined that increasing the pulse duration above about 2.3 ms began
25 damaging the vessel wall. It is believed that lysis is mechanical in nature and depends on various pulse parameters. Damage to the vessel (and to a probe in the case of invasive applications of ultrasound) is related to thermal effects, which are related to the accumulated energy transferred to a volume over time. Thus, by operating at a sufficiently short pulse duration, a clot can be lysed, without building up a
30 dangerously high amount of heat. It appears that operating above the cavitation

threshold, but less than about 50% of the pulse duration which can damage the vessel, can be both a safe and effective operating parameter.

Example 8

Referring to FIG. 9, the rate of clot mass dissolution as a function of
5 ultrasound intensity at the focal area was analyzed with $T = 8$ ms and $\tau = 1$ ms. A non-linear increase in dissolution rate with intensity was observed with fastest dissolution at intensities in the 1200 - 1400 W/cm² range.

Example 9

The use of an ultrasound imaging system similar to system 160 shown in
10 FIG. 1A provided additional information regarding the use of ultrasound for blood clot lysis. It is possible to visualize the clot during ultrasound application.

A bovine artery segment was filled with non-degassed PBS. The transducer was operated at frequency, $f = 650$ KHz, transducer excitation voltage, $U_{p/p} = 116$ volts, $T = 7$ ms and $\tau = 0.5$ ms. Bright reflection images corresponding
15 to cavitation were seen only at the posterior artery wall. This indicated that the transducer was located too close to the vessel. After the transducer was moved away from the vessel, reflection spots, indicating cavitation within the vessel were observed, indicating proper positioning of the transducer.

After the transducer was moved still farther away, bright reflection
20 corresponding to cavitation was observed only at the anterior artery wall, indicating that the transducer was located too far from the vessel. Thus, by combining conventional imaging ultrasound with non-invasive ultrasound lysis, it is possible to assure that the ultrasound focal point is at a desirable location within the body.

It has also been found that by changing the parameters, such as the pulse
25 duration, it is possible to adjust the size of the cavitation cloud detected with the imaging system to a desired size, such as not greater than the size of the clot or vessel.

Example 10

A successful non-invasive clot lysis procedure was conducted under the following conditions: driving frequency = 650 KHz, transducer excitation voltage =
30 116 V, pulse repetition period, $T = 7$ millisecond and pulse duration, $\tau = 0.5$ msec.

Referring to FIG. 10A, an ultrasound image of a clot (right side) and buffer solution (dark left side) within a bovine vessel is shown. The focal point of the therapeutic transducer was advanced along the longitudinal axis of the artery segment from left to right. Ultrasound treatment was stopped at approximately the middle of the clot.

5 Referring to FIG. 10B, it can be seen that the dark section indicative of liquid has grown from left to right in the vessel, and the clot has been reduced in size from the ultrasound treatment.

Example 11

Measurements of acoustic emission (microphone output) in the audible
10 range were conducted as a manifestation of the degree of cavitation activity by placing a microphone on a water filled tank. Referring to FIG. 11, microphone output was measured as a function of ultrasound peak intensity at $T = 7$ ms, for both $\tau = 0.070$ ms and $\tau = 0.100$ ms. As shown in FIG. 11, a well defined threshold to the peak intensity was observed.

15 In addition, above the intensity threshold, the correlation between cavitation activity and intensity was linear. For data points corresponding to $\tau = 70$ μ s, virtually no microphone output was observed until intensity exceeded approximately 1100 W/cm². For measurements made at $\tau = 100$ μ s, virtually no microphone output (cavitation) was observed until ultrasound peak intensity exceeded
20 about 600 W/cm².

As shown, cavitation activity increased with increased pulse duration. It was also observed that above the threshold, cavitation initiation was random, occurring in the range of $I = 600 - 2800$ W/cm². However, if, for example, cavitation initiated at $I = 2,000$ W/cm², microphone output would always be in the high range
25 relative to if cavitation initiated at $I = 800$ W/cm². It was also determined that after cavitation is initiated, the intensity can be decreased. Although cavitation activity will decrease, cavitation was maintained at the intensity shown in FIG. 11.

It was also determined that placing a microphone on the outside of the body of the subject receiving ultrasound treatments can provide an excellent method of
30 obtaining feedback regarding whether cavitation is occurring. Thus, if an operator is

applying ultrasound to a subject, he can watch or listen to a display from the microphone and determine whether cavitation is occurring under parameters where cavitation should be occurring. In addition, the microphone output can be fed to a data processor, which can display a warning signal or deactivate the ultrasound device if the device is fully powered, but cavitation is not being detected by the microphone. Also, the feedback can permit an operator to reduce power to the transducer to obtain the minimal amount of power needed to sustain cavitation. This procedure can also be performed while detecting cavitation with an ultrasound imaging transducer.

Example 12

Referring to FIG. 12, a comparison was conducted between cavitation activity produced in a buffer and in a clot for $T = 7$ ms and $\tau = 0.1$ ms. Both the threshold and slope of the increase of cavitation activity with intensity were different for the buffer solution and the clot. The linear correlation (R) of the buffer and clot plots were $R = 0.94$ and $R = 0.61$, respectively.

After cavitation had been initiated and detected either audibly or with an imaging transducer, the voltage can be decreased to decrease the ultrasound intensity, but maintain cavitation, i.e., it is an inertial phenomenon. Thus, in order to promote additional safety of operation, once cavitation of a clot has begun, the intensity can be decreased, often by as much as 50% or more to maintain cavitation within the blood vessel but diminish a chance to injure the vessel itself.

Cavitation in blood and buffer solution was analyzed for degassed and non-degassed media. Operating conditions were $T = 7$ msec and $\tau = 0.1$ msec. The cavitation threshold for a degassed medium is higher than in a non-degassed medium. Also, there was no difference in cavitation threshold between blood and the buffer solution for the parameters tested.

The cavitation threshold for non-degassed buffer and blood was in the range of 1000 to 1500 W/cm^2 , closest to about 1200 W/cm^2 . With respect to degassed buffer and blood, the cavitation threshold centered around 2000 W/cm^2 .

The cavitation thresholds for non-degassed and degassed clots were also analyzed at $T = 7\text{ms}$ and $\tau = 0.1\text{msec}$. As with the above experiments, the cavitation threshold of a degassed sample was higher than the non-degassed sample.

Example 13

5 Referring to FIG. 13, the activity of cavitation in blood, as a function of ultrasound intensity, was analyzed at $\tau = 40\text{ }\mu\text{s}$ for pulse repetition periods of $T = 8\text{ ms}$, 16 ms , 20 ms , 30 ms , 40 ms , 50 ms , 70 ms , and 90 ms as shown in curves 751-758, respectively. As shown in FIG. 13, there is an intensity threshold for inducing cavitation and the threshold was inversely proportional to pulse repetition period. For
10 $T = 8\text{ ms}$, cavitation occurred at an intensity of about $I = 1250\text{ W/cm}^2$ and for $T = 90\text{ ms}$, cavitation was first observed at $I = 1750\text{ W/cm}^2$.

Example 14

Referring to FIG. 14, an experiment similar to that discussed with reference to FIG. 13 was performed, in which blood was tested at $\tau = 150\text{ }\mu\text{s}$ and pulse
15 repetition periods of 8 ms , 16 ms , 20 ms , 30 ms , 40 ms , 50 ms , 70 ms and 90 ms , which are depicted by curves 451 through 458, respectively. Longer pulse repetition periods were associated with higher intensity requirements to initiate cavitation and higher cavitation activity.

Example 15

Referring to FIG. 15, the influence of pulse duration on cavitation
20 activity was analyzed. Shorter pulse durations were associated with greater cavitation activity. Also, a pulse repetition period $T =$ between about 10 ms and 50 ms created maximum cavitation activity for pulse durations from about $150\text{ }\mu\text{s}$ to about $700\text{ }\mu\text{s}$, correlating to duty ratios ranging from about 15 to 500.

A buffer solution was subjected to ultrasound at an intensity of 2400 W/cm^2 . The pulse repetition period was varied from about $T = 5\text{ ms}$ to about 90 ms
25 for the following pulse durations: 0.100 ms (curve 151), 0.150 ms (curve 152), 0.250 ms (curve 153), 0.400 ms (curve 154), 0.700 ms (curve 155).

The experiment described above was repeated with pulse durations of 0.100 ms , 0.150 ms , 0.250 ms , 0.400 ms and 0.700 ms at an intensity $I = 2200\text{ W/cm}^2$.
30 The results are similar to those shown in FIG. 15, except that the cavitation activity

decreased slightly with the decreased intensity. Maximum cavitation activity occurred in the range $T < 50$ ms.

An experiment similar to that discussed above was performed at an intensity of $I = 2080 \text{ W/cm}^2$ at pulse durations of 0.100 ms, 0.150 ms, 0.250 ms, 0.400 ms, and 0.700 ms, respectively. Again, cavitation activity decreased with decreased ultrasound intensity and optimal pulse repetition periods were in the range $T < 40$ ms. Shorter durations were associated with higher activity. As ultrasound intensity and hence cavitation activity decreased, the width of the range of optimal pulse repetition periods also decreased.

An experiment similar to that discussed with reference to FIG. 15 was performed, in which ultrasound intensity was set at $I = 1800 \text{ W/cm}^2$. Maximum cavitation occurred above $T < 30$ for all but experiments run at a pulse duration of 0.700 μs , which exhibited cavitation to about $T = 50$ ms.

Example 16

Another experiment similar to that discussed with reference to FIG. 15 was performed, except that the medium tested was blood, rather than a buffer solution. Referring to FIG. 16, the intensity was set at 2400 W/cm^2 and results are shown for pulse durations of 0.100 ms, 0.150 ms, 0.250 ms, 0.400 ms and 0.700 ms for curves 251, 252, 253, 254 and 255 respectively. The parameters for causing cavitation in blood were found to be different than those for causing cavitation in the buffer solution. For example, cavitation in blood was sustained over a much wider range of pulse repetition periods, to over $T = 100$ ms. Again, however, the shorter pulse durations exhibited higher microphone output.

Example 17

FIG. 17 shows cavitation as a function of pulse duration for a blood sample (curve 351) and a buffer sample (curve 352), at $T = 50$ ms and intensity $I = 2400 \text{ W/cm}^2$. Optimal cavitation for the blood sample was in a pulse duration range of about $\tau = 100$ to $250 \mu\text{s}$ and a duty ratio of about 500 to about 200. It was evident that cavitation could still be achieved above $\tau = 700 \mu\text{s}$. For the buffer solution, the range

of most effective pulse durations was narrower, and ranged from about 80 to about 150 μ s. However, it was evident that cavitation would still occur above $\tau = 700 \mu$ s.

The experiment discussed with reference to FIG. 17 was repeated at $T = 8$ ms and the same intensity (2400 W/cm^2). The shorter pulse repetition periods slightly decreased the cavitation activity for the blood sample and increased the cavitation activity for the buffer sample, relative to the values shown in FIG. 17 and caused the cavitation activity for the buffer samples to be more similar. Cavitation was sustained from $\tau = 50$ to 700μ s. Accordingly, different materials will exhibit different activity with respect to different pulse repetition periods. Thus, it can be advantageous to lyse a clot with parameters which cause high cavitation in blood, and will have a less pronounced effect on the blood vessel.

Example 18

Referring to FIG. 18, the efficiency of clot lysis was analyzed by measuring percentage of clot weight loss as a function of ultrasound intensity for both a non-degassed (curve 551) and a degassed blood clot sample (curve 552). Lysis was performed with $T = 7$ ms and $\tau = 0.1$ ms, at $V_m = 15$ mm/min. Percentage of weight loss was determined by visual inspection and accordingly, the data are reasonable approximations. As shown in FIG. 18 the non-degassed clot was lysed at lower ultrasound intensities, with intensities above $I = 1600 \text{ W/cm}^2$ judged effective on the non-degassed sample and above $I = 2200 \text{ W/cm}^2$ on the degassed sample. Thus, the T and τ values and a duty cycle of 70 were deemed suitable.

Example 19

Referring to FIG. 19A, a clot was lysed at $I = 1900 \text{ W/cm}^2$ at pulse durations of 100, 200 and 300 μ s. One hundred percent clot dissolution was achieved at 200 and 300 μ s. Referring to FIG. 19B, under the same conditions, except for a reduction of intensity to $I = 1400 \text{ W/cm}^2$, optimum clot dissolution was achieved at $\tau = 200 \mu$ s, with clot lysis at reduced efficiency at $\tau = 100$ and 300μ s. As shown, at lower intensities, high efficiency was achieved at $T/\tau = 35$, compared with $T/\tau = 70$ or 23.

Referring to FIG. 20A, at $T = 14$ ms and $V = 15$ mm/min and an intensity of $I = 1400$ W/cm², the results of curve 571, were achieved. Referring to FIG. 20B, when τ was set at 200 μ s, V was set at 10 mm/min and the pulse repetition period was varied from about 2.5 to 20, optimal clot dissolution was achieved at $T = 5$ ms, or $T/\tau = 25$, in a range of about 12 to 50, as shown by curve 572. Clot dissolution also be achieved above $T = 20$ ms.

Referring to FIG. 20C, curve 581, $T = 5$ ms, $\tau = 0.2$ ms and $V = 10$ mm/min, pulse duration was varied from 100 μ s to 300 μ s at an ultrasound intensity of 1300 W/cm². Optimal efficiency was achieved at $\tau = 200$ μ s, with the most efficient range from about 175 to 225 μ s. Lysis was effective above $\tau = 0.150$ ms.

Referring to FIG. 21, curve 582, intensity of ultrasound was varied from about 900 W/cm² to about 1700 W/cm². The cavitation threshold occurred at approximately 1250 W/cm² with maximum efficiency of intensities over 1300 W/cm² at $T = 5$ ms and $\tau = 0.2$ ms. Increasing intensity maintained full clot dissolution.

15 Example 20

Referring to FIG. 22, the efficiency of clot lysis was assessed by measuring the weight of unlysed clot after ultrasound application, as a function of ultrasound intensity. Parameters were $T = 5$ ms, $\tau = 0.2$ ms, $f = 650$ KHz, $V = 5$ mm/min and intensity ranged up to 2500 W/cm². Unlysed clot material was separated with an 80 μ m size filter. As shown in FIG. 22, above the threshold for clot lysis, only a small portion of the clot remained unlysed. At the parameters investigated, this intensity threshold was in the range 750 to 1250 W/cm².

The following examples present data illustrating from the application of ultrasound with a probe designed for the invasive application of ultrasound operated at about 44.4 KHz. Ultrasound was applied with a probe, similar to that depicted in U.S. Ser. No. 08/858,247, filed May 19, 1997 (the contents of which are incorporated herein by reference), having a proximal transducer coupled to an elongated transmission member with a distal tip constructed to cause cavitation within a blood

vessel when activated by ultrasound transmitted from the transducer through the transmission member.

A non-limiting embodiment of an invasive-type ultrasound probe is illustrated generally as probe 1200 in FIG. 22, and in a copending application entitled
5 COOLING SYSTEM FOR ULTRASOUND DEVICE under Application Serial No. 60/047,022, filed May 19, 1997, the contents of which are incorporated herein by reference.

Probe 1200 is formed with a tapered member 1225, formed with a proximal end 1229 of diameter A_i constructed to be coupled to a source of ultrasound
10 energy such as a transducer 1248. When coupled to a source of ultrasound energy, proximal end 1229 is preferably located at a displacement maximum relative to the standing ultrasound wave supported by the overall device. From proximal end 1229, tapered member 1225 tapers to a reduced diameter distal end of diameter A_r .

Proximal end 1229 must be large enough to receive sufficient energy to
15 treat a thrombus, occlusions and the like. However, in order to provide optimal flexibility, it is desirable to reduce the diameter of distal portions of probe 1200 as much as possible, without significant loss of energy, strength or guidability. Furthermore, the reduction in diameter is preferably accomplished in such a manner as to amplify, or increase the amplitude of, the ultrasound vibrations.

20 Ultrasound device 1200 is understood to operate in the resonant frequency mode; i.e., it supports a standing wave when energized by ultrasonic stimulation at proximal end 1229. Consequently, it is preferred that a cavitation tip 1250 is located at a displacement maximum (anti-node).

To dissipate energy lost as heat, a probe in accordance with the
25 invention can be bathed with a coolant. The coolant can be directed over and around the probe, for example, by incorporating a sheath 1245 around some or all sections of the probe. Sheathing 1245 may be affixed to the probe at one or more of the displacement nodes of the standing wave. Additional sheathing may be incorporated for providing a passageway for a guidewire or other auxiliary tool which may serve to

steer or position the device to its intended location. Sheathing 1245 is formed of a high-strength, thin-walled, low-friction material, preferably polyimide.

Probe 1200 includes a horn 1225, having a tapered section T and a first constant diameter section S, is constructed to be coupled to an ultrasound energy source. Ultrasound energy is provided by the controller at a power source 1246 via a coaxial cable 1247 to a quick disconnect 1249, which connects coaxial cable 1247 to transducer 1248. Transducer 1248 is intimately connected to horn 1225. Probe 1200 also includes a transmission member 1240 coupled to horn 1225 and a tip 1250 coupled to the distal end of transmission member 1240. Ultrasound energy sources disclosed in U.S. Patent No. 5,269,297, and in a copending application entitled FEEDBACK CONTROL SYSTEM FOR ULTRASOUND PROBE under Application Serial No. 60/046,938, filed May 19, 1997, the contents of which are incorporated herein by reference, are suitable.

Tip 1250 is coupled to three fine wires joining section 1240 and tip 1250 by means of three openings in tip 1250. In a preferred embodiment, the three openings in tip 1250 are spaced so as to form an equilateral triangle, concentric with the central axes of coupling tip 1250. Tip 1250 may also be provided with an opening for a guidewire, and a guidewire tube may be installed in the opening and extended proximally from the distal end. The fine wires may be separately sheathed, and any sheathing may extend between tip 1250 and a coupling joint. Wire 1240 may also be sheathed and the sheathing may be connected to the separate sheathing of the fine wires and may extend proximally to a coolant port through which coolant may be injected to bathe all or part of the transmission member.

The entire probe was placed in a straight configuration in a Plexiglas tube with an inner diameter of 3.5 mm and the tube was placed inside a water tank. A microphone was placed on the outside of the water tank and measured acoustic output which correlates to cavitation activity. The probe was operated in both continuous mode and pulse mode under various operating parameters and data was compiled.

Example 21

Referring to FIG. 24, at $T = 1000$ ms and $\tau = 500, 250, 750, 125, 875$,

164 ms, corresponding to curves 601-607 respectively and curve 608 corresponding to the probe activated in continuous mode, a cavitation threshold existed in the range 5 to 10 watts for pulsed mode of operation and non-degassed water.

Example 22

5 An additional experiment was run in non-degassed water at $T = 500$ ms and $\tau = 250, 125, 64$ and 32 ms. A control was also run in continuous mode. The results were similar to those shown in FIG. 24, with a threshold to cavitation in the range 10 to 20 watts and relatively no cavitation generated from operation in the continuous mode at up to 20 watts.

Example 23

 Referring to FIG. 25, an experiment similar to that discussed with reference to FIG. 24 was conducted, wherein non-degassed water received ultrasound from an invasive-type probe, but at $T = 250$ ms. Electric power was increased over the range 0 to 40 watts at $\tau = 125, 64, 32$ and 16 ms, corresponding to curves 125, 64, 32
15 and 16 ms, corresponding to curves 651, 652, 653 and 654, respectively. Curve 655 shows operation in the continuous mode. As shown in FIG. 25, an ultrasound threshold occurred at about 20 watts and there was essentially no cavitation generated from the continuous mode operation at this power level.

Example 24

20 Still another experiment was conducted, in which ultrasound was applied from an invasive-type transducer to non-degassed water at $T = 125$ ms and $\tau = 64, 32, 16$ and 8 ms. Cavitation initiated in the range 15 to 20 watts for the pulse mode of operation, but not in the continuous mode operation, demonstrating advantages of pulsed operation in accordance with the invention.

Example 25

25 Referring to FIG. 26, the procedure discussed with reference to FIG. 24 was performed at $T = 64$ ms. Pulse durations of $\tau = 32, 16, 8$, and 4 ms are shown in FIG. 25 as curves 661, 662, 663 and 664, respectively. Continuous mode operation is shown as curve 665. The cavitation threshold occurred in the range 15 to 20 watts for

the pulsed mode of operation, but not the continuous mode of operation, demonstrating advantages of pulsed operation in accordance with the invention.

Example 26

Referring to FIG. 27, the above procedure was repeated at $T = 32$ ms and
5 $\tau = 16, 8$ and 4 ms, corresponding to curves 671, 672 and 673, respectively. Continuous mode operation is shown by curve 674. A cavitation threshold occurred in the range of about 15 to 20 watts for pulsed operation, but with less overall cavitation activity than for some of the longer pulse durations. It is believed that the liquid medium requires a recovery period for optimum cavitation efficiency.

10 Comparative Example 27

The invasive-type probe was operated under 18 watts of power. A thermocouple in contact with the tip inside the tube provided real time data with respect to temperature. Referring to FIG. 28, the system was initially at 37°C , 10 ml/min of 24°C cooling water was pumped through the tube. As shown in FIG. 28,
15 this reduced temperature at the probe tip to approximately 24°C . At point 681, the probe was turned on and activated with 18 watts of power. This quickly raised the temperature to over 41°C (point 682).

At point 683, power was turned off and the temperature quickly returned to the cooling water temperature. At point 684, cooling water was turned off and the
20 probe returned to approximately 34.4°C . At point 685, cooling water was turned on and the temperature of the probe quickly returned to approximately 27° .

At point 685, the probe was turned back on and the temperature quickly rose to above 41°C . After the power was turned off, the temperature of the probe returned to the temperature of the cooling water and then returned to the temperature
25 of the tank after the cooling water was turned off.

Example 28

Considerably different results were achieved when the probe was operated in pulse mode at a duty cycle of 8 ($T = 250$ ms $\tau = 32$ ms) when 24°C cooling water at 10 ml/min was turned on, the temperature of the probe quickly
30 dropped to about 24°C . At point 691 power was turned on at a level of 20 watts. As

shown in FIG. 29, the probe temperature increased to only slightly over 27°C, for a temperature increase of only about 3°C. At point 682, power to the probe was turned off and at point 683, the cooling water was turned off. At point 684, cooling water was turned back on and at point 685, power to the probe was turned back on. The probe was operated at 18 watts until it was turned off at point 686. As shown, probe temperature only increased about 2°C.

Similar results were achieved at a duty cycle of 16 ($T = 250$, $\tau = 16$) (FIG. 30). At point 691, cooling water was turned on and at point 692, the probe was activated with 20 watts of power and turned off at point 693. As shown, probe temperature increased only 1 to 2°C. At point 694, cooling water was turned back on, the probe was turned on with 18 watts of power at point 696 and turned off at point 697. As shown, only a minimal increase in temperature occurred.

Tables 1 and 2 below provide evidence from additional experiments showing a minimal temperature rise when the probe is operated in a pulsed mode, particularly at a duty cycle ratio of 8 or more. In view of their minimal temperature increase using the described pulsing parameters in conjunction with the lower cavitation threshold and high cavitation activity, it is believed that invasive-type probes can be operated without cooling fluid and also, without a covering sheath. This will permit the use of substantially smaller guide catheters in view of an overall reduction in the outer dimensions of the probe. Another advantage is a considerable reduction in metal fatigue.

Table 1
Study on the temperature rise at different flow rates of the cooling buffer
and at different excitation modes.

#	Flow Rate	Duty Cycle	Power	Temp Rise	Max Temp
1	10	Continuous	18	16.8	41.7
2	10	Continuous	18	15.4	41
3	10	8	20	2.4	28.1
4	10	8	18	1.7	27.6
5	10	16	20	1.2	27.1
6	10	16	18	0.7	26.6
7	10	8	30	4.6	31.8
8	10	8	30	4.1	31.6
9	10	8	40	5.3	33.3
10	10	8	40	5.3	33.3
11	10	16	30	3.8	29.7
12	10	16	30	4.1	29.2
13	10	16	40	4.8	30.8
14	10	16	40	4.6	30.7
15	5	8	30	8.2	35
16	5	8	30	8.4	35
17	5	8	30	7.2	36.2
18	5	8	30	7.2	36.1
19	5	16	30	4.6	33.5
20	5	16	30	4.3	33.5
21	5	16	40	8.2	37.5
22	5	16	40	6.2	34.1
23	2.5	16	30	3.7	35.7
24	2.5	16	30	4.1	35.7
25	0	16	20	3.1	39.8
26	0	16	20	3.1	39.8
27	0	16	30	4.6	41.1
28	0	16	30	4.1	40.9
29	0	16	40	Destruction	—
30	10	Continuous	18	16.1	45.8
31	10	Continuous	18	16.8	44.3
32	10	Continuous	18	17.8	45.3
33	10	16	18	2.2	30
34	10	16	18	1.7	30.5
35	10	16	18	2.6	29.8
36	10	8	18	1.2	29.9
37	10	8	18	1.2	29.9
38	10	8	18	1.2	29.9
39	5	16	18	1.5	31.8

#	Flow Rate	Duty Cycle	Power	Temp Rise	Max Temp
40	5	16	18	1.7	32.1
41	5	16	18	1.5	31.9
42	0	16	18	2.4	39.6
43	0	16	18	2.4	39.6
44	0	16	18	2.6	39.8
45	0	16	18	2.6	39.8
46	0	16	18	2.6	39.8
47	0	16	18	2.6	39.8
48	10	16	18	1	28.8
49	10	16	18	1.2	29.1
50	10	16	18	1.2	29.1
51	5	16	18	1.5	31.4
52	5	16	18	1.7	31.4
53	5	16	18	1.7	31.4
54	10	8	18	1.2	28.9
55	10	8	18	1	29.1
56	10	8	18	1.2	29.4
57	10	Continuous	18	16.6	43.9
58	10	Continuous	18	16.1	43.6
59	10	Continuous	18	16.6	43.6

Table 2
Study on the temperature rise at different flow rates of the cooling buffer
and at different excitation modes.

#	Flow Rate ml/min	Duty Cycle	Pulse Rep. Period (mS)	Pulse Length (mS)	Power (watt)	Frequenc y (KHz)	Temperature Rise (grad)	Max Temp (grad)
1	10	Continuous	-	-	18	44.6	16.1	41.3
2	10	8	256	32	20/18	44.6	2.4/1.7	27.9
3	10	16	256	16	20/18	44.6	1.2/1.0	26.9
4	10	8	256	32	30	44.4	4.6	31.7
5	10	8	256	32	40	44.4	4.8	33.3
6	10	16	256	16	30	44.4	2.9	29.5
7	10	16	256	16	40	44.4	4.3	38
8	5	8	256	32	30	44.4	7.9	35
9	5	8	256	32	30	44.3	7.2	36.2
10	5	16	256	16	30	44.3	3.8	33.5
11	5	16	256	16	40	44.3	7	36
12	2.5	16	256	16	30	44.3	3.8	35.7
13	0	16	256	16	20	44.3	3.1	39.8
14	0	16	256	16	30	44.3	4.3	41
15	0	16	256	16	40	44.3	Destruction	-
16	10	Continuous	-	-	18	44.5	16.9	45
17	10	16	256	16	18	44.5	2.2	30
18	10	8	256	32	18	44.5	1.2	29.9
19	5	16	256	16	18	44.5	1.6	31.9
20	0	16	256	16	18	44.5	2.5	39.7
21	10	16	256	16	18	44.5	1.1	29
22	5	16	256	16	18	44.5	1.6	31.4
23	10	8	256	32	18	44.5	1.1	29.1
24	10	Continuous	-	-	18	44.5	16.4	43.8

Example 29

Referring to FIGS. 32A, 32B and 32C, it can be seen that the size of the cavitation cloud is related to pulse duration. For example, with the ultrasound generating transducer operating at 40 W/cm² average intensity in the focal area, the size of the cavitation cloud increased with increased pulse duration.

Referring to FIG. 32A, a small cavitation cloud 3201(a) can be seen with an ultrasound imaging transducer when the ultrasound generating transducer was operated at a pulse duration of 50 μ sec. An operator viewing the procedure could determine that cloud 3201 was smaller than a clot 3302 attached to a vessel wall 3203 and decide to increase the pulse duration.

Referring to FIG. 32B, it can be seen that when the pulse duration was increased to 250 μ sec, a medium sized cavitation cloud 3201(b) was generated. An operator could determine that cloud 3201(b) matched the size of clot 3202 and was within vessel 3203.

Referring to FIG. 32C, when the pulse duration was increased to 450 μ sec, an operator monitoring the procedure with an ultrasound imaging transducer could observe that a large cavitation cloud 3201(c) was created not only within, but also outside vessel 3203. Therefore, an operator or even an automated system could detect that the cavitation cloud was undesireably large and reduce the pulse duration and cavitation cloud size to levels such as those shown in FIG 32B.

It is understood that the techniques described for the invasive and non-invasive application of ultrasound are also applicable to systems that promote or focus ultrasound energy to enhance the absorption of drugs, induce apoptosis in cells, and/or treat tissue, tumors, obstructions, and the like, within and without the body, systems to be utilized in or for laproscopic surgery, for ultrasonic scalpels, and to induce tissue hyperthermia such as for cancer radiation therapy, for example. Furthermore, drugs, such as streptokinase, urokinase, whose function or efficacy would be enhanced by ultrasound or that would enhance the application of ultrasound at the treatment site, may be infused within the coolant fluid for cooling the ultrasound probe or delivered

through a separate passageway within or without the ultrasound probe to the treatment site.

The following is a partial list of applications for pulsed ultrasound:

Clot lysis	Cell function manipulation (eg. migration, adhesion, etc.)
Plaque ablation	Drug delivery manipulation
Coagulation	Drug activity enhancement
Cancer treatment	Biological product manipulation (eg. genes, anti-sense DNA)
	Phonophoresis
Induction of Apoptosis	Molecule manipulation
Induction of Necrosis	Cavitation initiation manipulation
Liposuction/Lipolysis	Cavitation sustaining manipulation
Induction of Angiogenesis	Heat generation manipulation

5 It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained and, since certain changes may be made in the above composition of matter without departing from the spirit and scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

10 It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the invention which, as a matter of language, might be said to fall therebetween.

CLAIMS

What is claimed is:

1. A method of applying therapeutic ultrasound to a location within a body, comprising: activating a transducer with selected activation parameters to produce ultrasound and directing this ultrasound to a location within a body; monitoring the level of cavitation at the location within the body; adjusting the location of the ultrasound within the body or the activation parameters until a first level of cavitation is detected at a selected location within the body; and adjusting the parameters to change the level of cavitation at the selected location based on information obtained through said monitoring the level of cavitation.
2. The method of claim 1, wherein the ultrasound is directed to the location within the body in an invasive manner, with an ultrasound device which is inserted into the body.
3. The method of claim 1, wherein the ultrasound is directed to the location within the body with a non-invasive ultrasound producing device.
4. The method of claim 2, wherein the power to the transducer is reduced after cavitation is detected at the selected location.
5. The method of claim 3, wherein the power to the transducer is reduced after cavitation is detected at the selected location.
6. The method of claim 2, including the step of applying a microphone to the body, wherein said monitoring of the presence or lack of cavitation is performed with the microphone applied to the body.
7. The method of claim 3, including the steps of directing an ultrasound imaging transducer to the selected location, wherein the monitoring of the level of cavitation at the selected location is performed with the ultrasound imaging transducer.
8. The method of claim 7, wherein the ultrasound is delivered to the body in pulses and causes the formation of a cavitation cloud at the selected location and the duration of the pulses is adjusted to change the size of the cavitation cloud to a selected size in response to the monitoring.

9. The method of claim 4, wherein the ultrasound is causing cavitation and the amount of cavitation caused is reduced automatically if the amount of cavitation monitored exceeds a predetermined amount.

10. The method of claim 5, wherein the ultrasound is causing cavitation and the amount of cavitation caused is reduced automatically if the amount of cavitation monitored exceeds a predetermined amount.

11. A system for delivering ultrasound energy into a body, comprising:

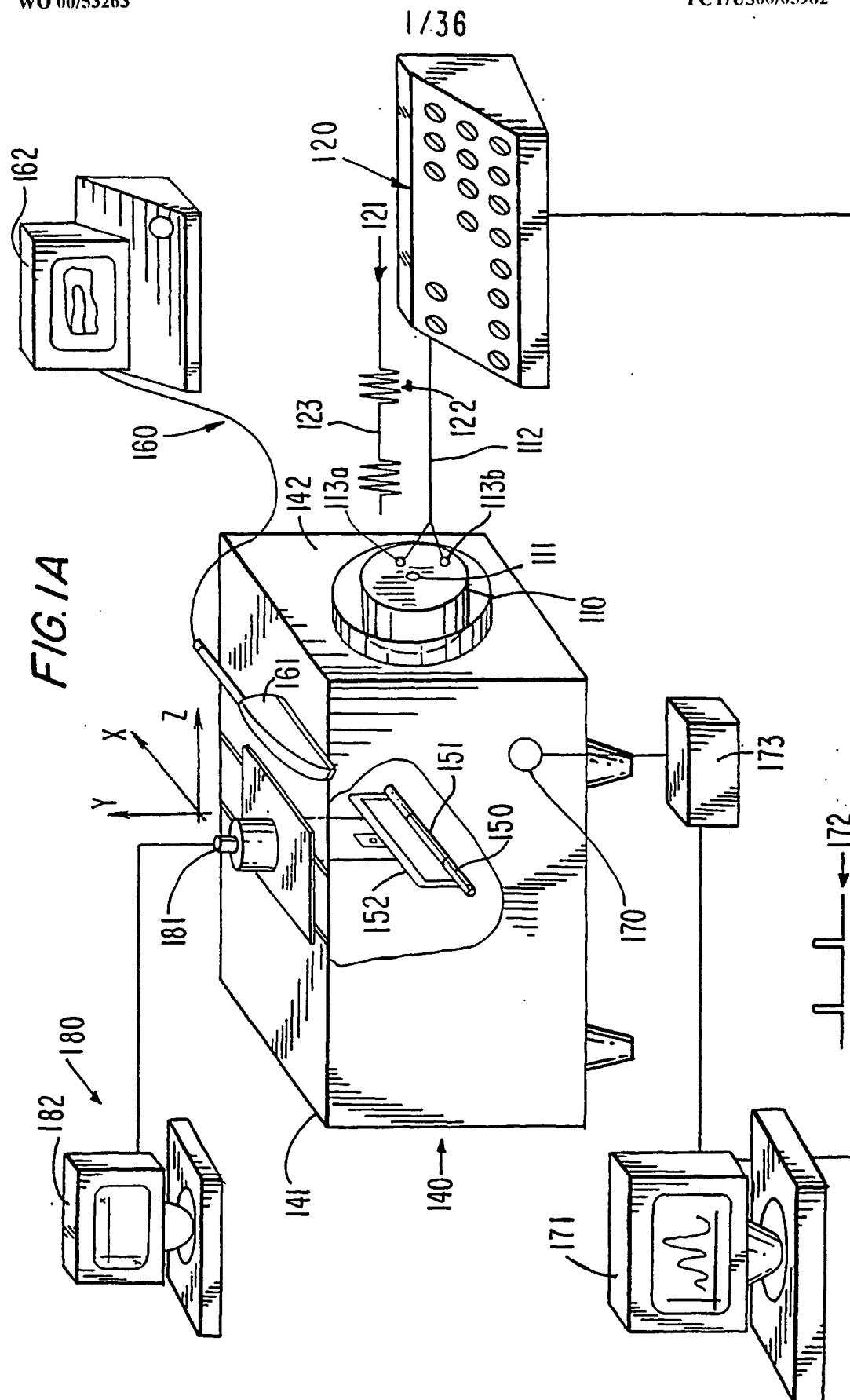
a signal generator, a transducer coupled to the signal generator, and a transmission member coupled to the transducer; the signal generator, transducer and transmission member constructed and arranged to transmit ultrasound to a location within the body by inserting at least a portion of the transmission member into the body; and

a sound detection device and a display capable of detecting the sound caused by cavitation within the body generated by ultrasound transmitted via the transmission member and displaying the presence of sound caused by the presence of cavitation.

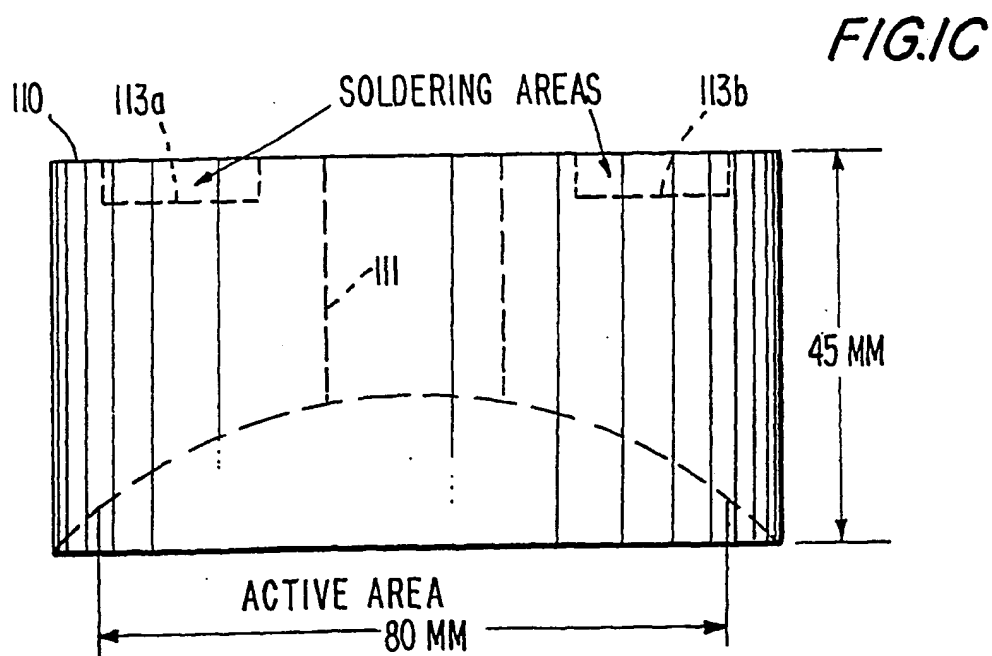
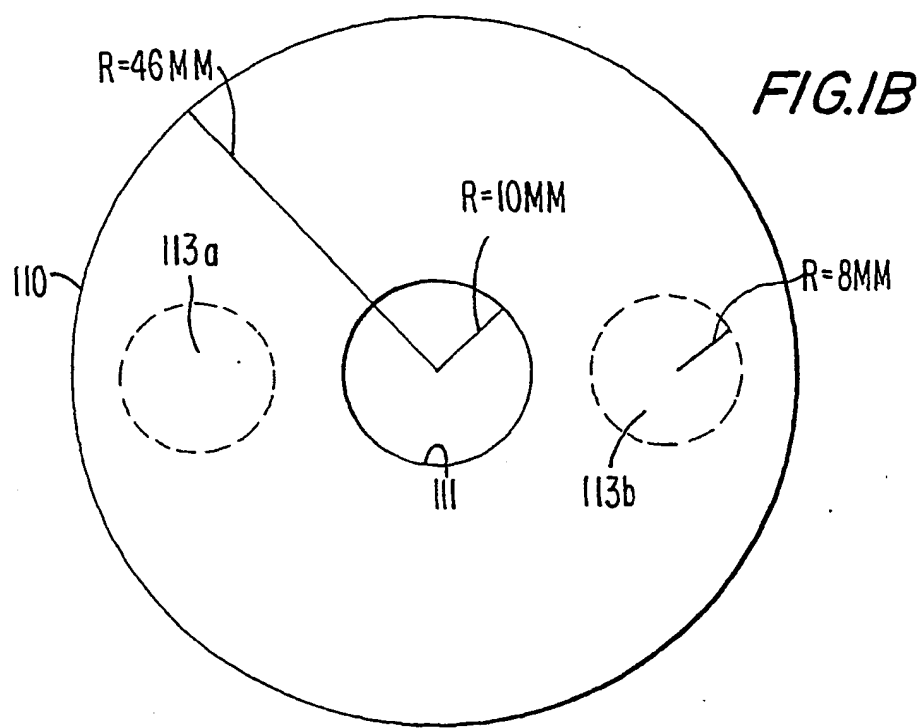
12. The system of claim 11, wherein the power of the transducer is decreased automatically when the sound detected exceeds a predetermined value.

13. A system for delivering ultrasound into a body, comprising:

a transducer unit formed with an ultrasound producing transducer capable of transmitting ultrasound into a body non-invasively; an ultrasound imaging transducer, the imaging transducer adapted to detect cavitation caused within a body by ultrasound from the ultrasound transducer and generating a signal responsive to the presence and intensity of cavitation caused within the body; a control unit responsive to the signal from the imaging transducer, adapted to generate a control signal when the signal from the imaging transducer indicates ultrasound detected at an intensity above a preselected level; the system constructed so that the power of the ultrasound transmitted to the body is reduced in response to the control signal.

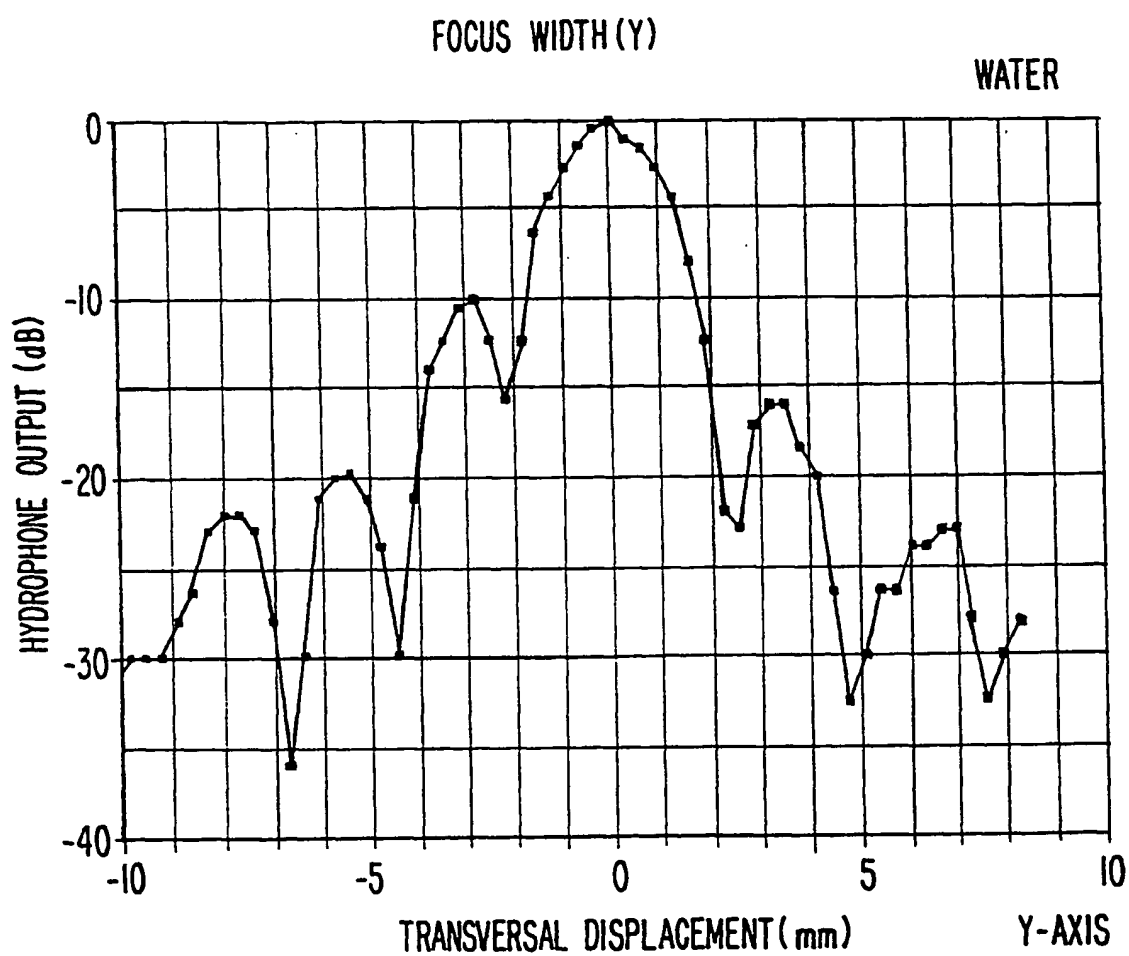


2 / 36

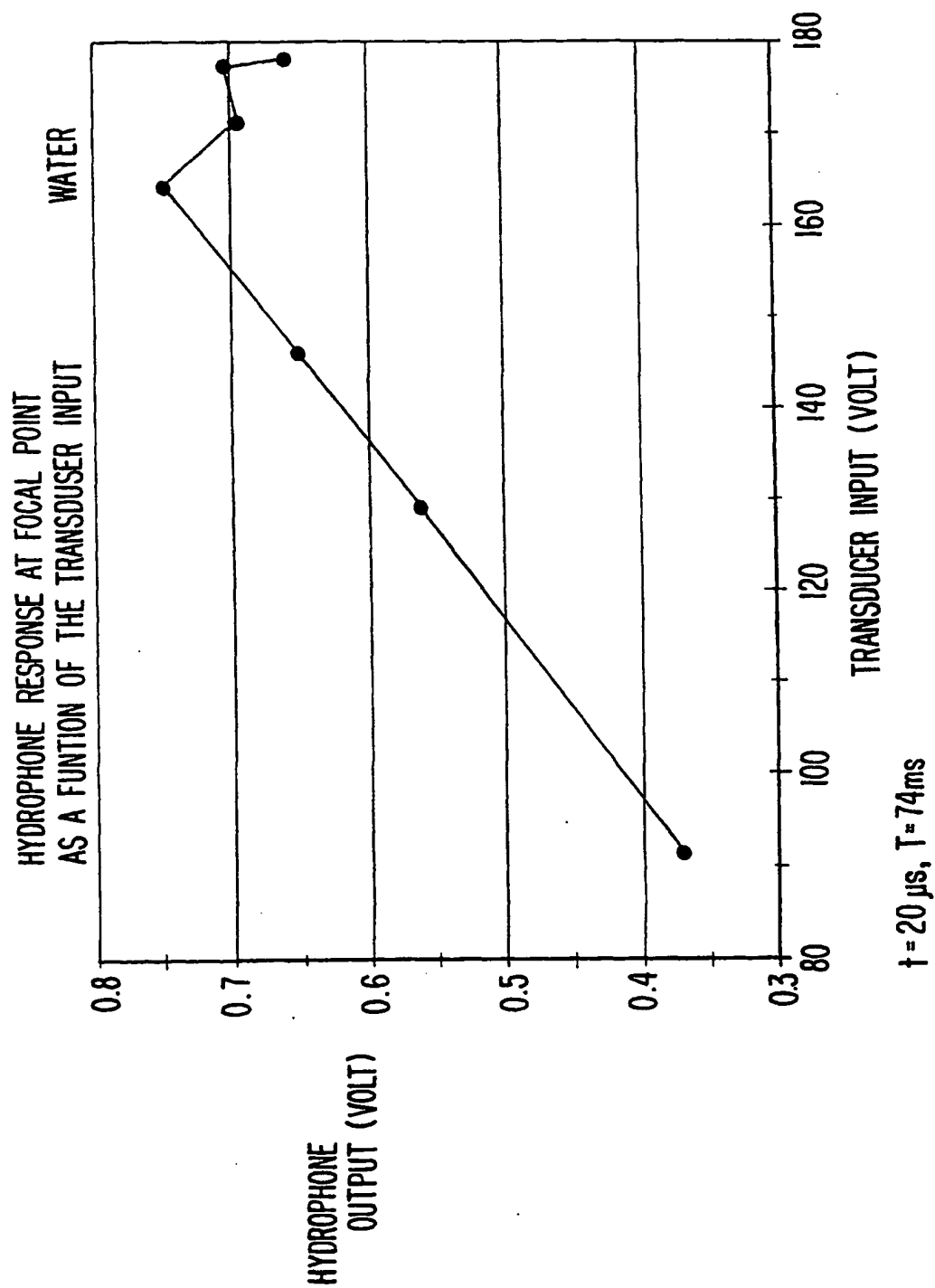


3/36

FIG. 2

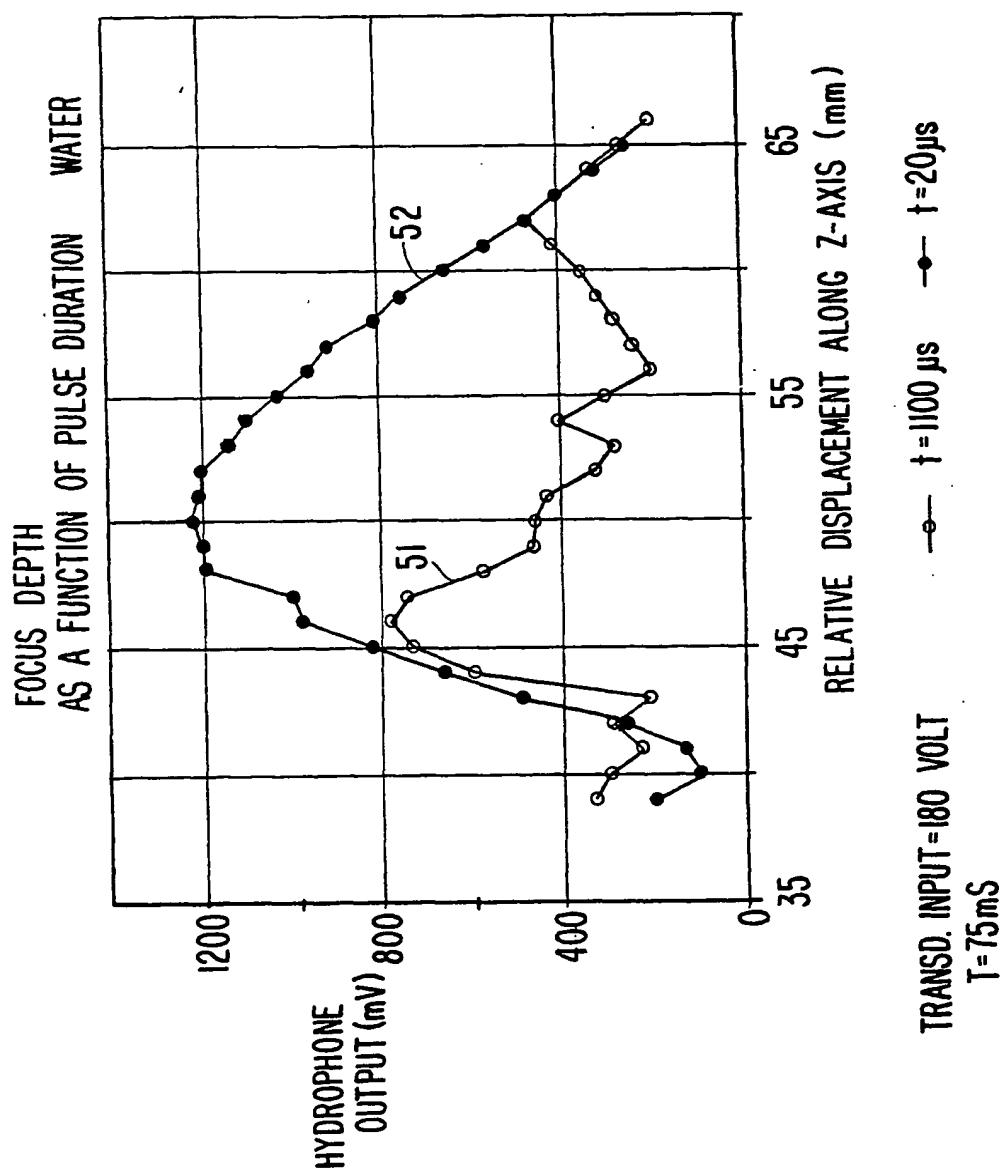
 $t = 20 \mu s, T = 74 ms, 46V$

4/36

FIG. 3

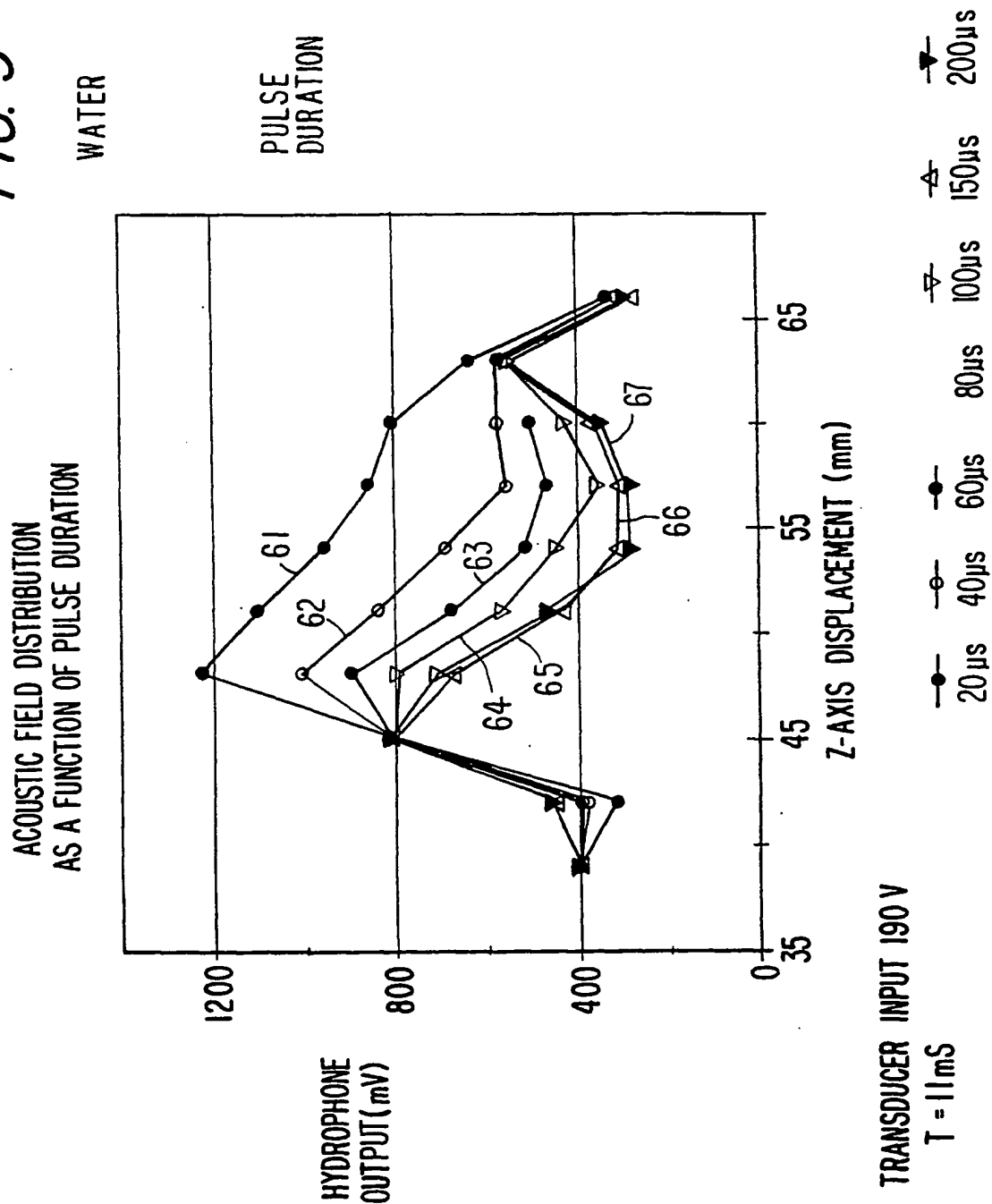
5/36

FIG. 4



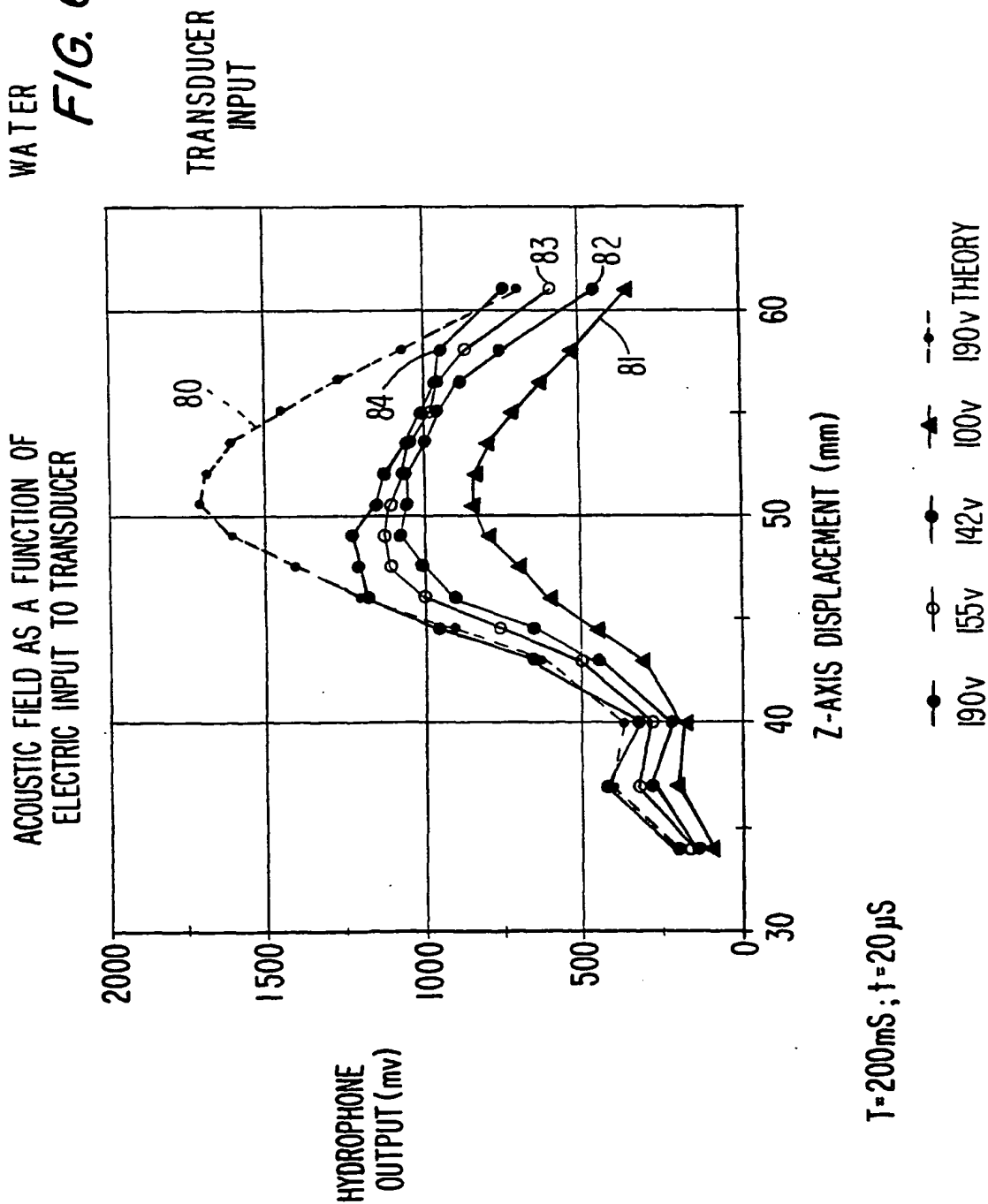
6/36

FIG. 5



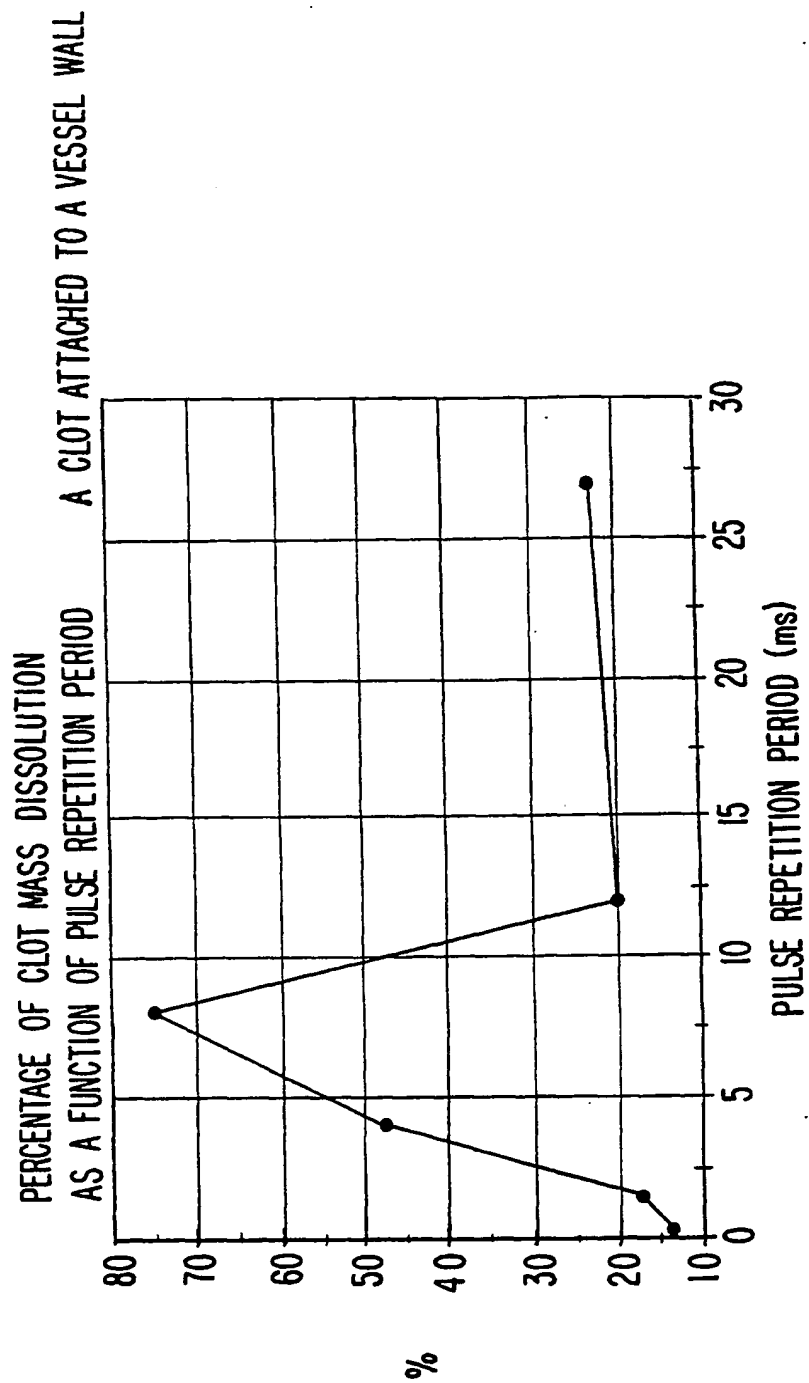
7/36

WATER
FIG. 6



8/36

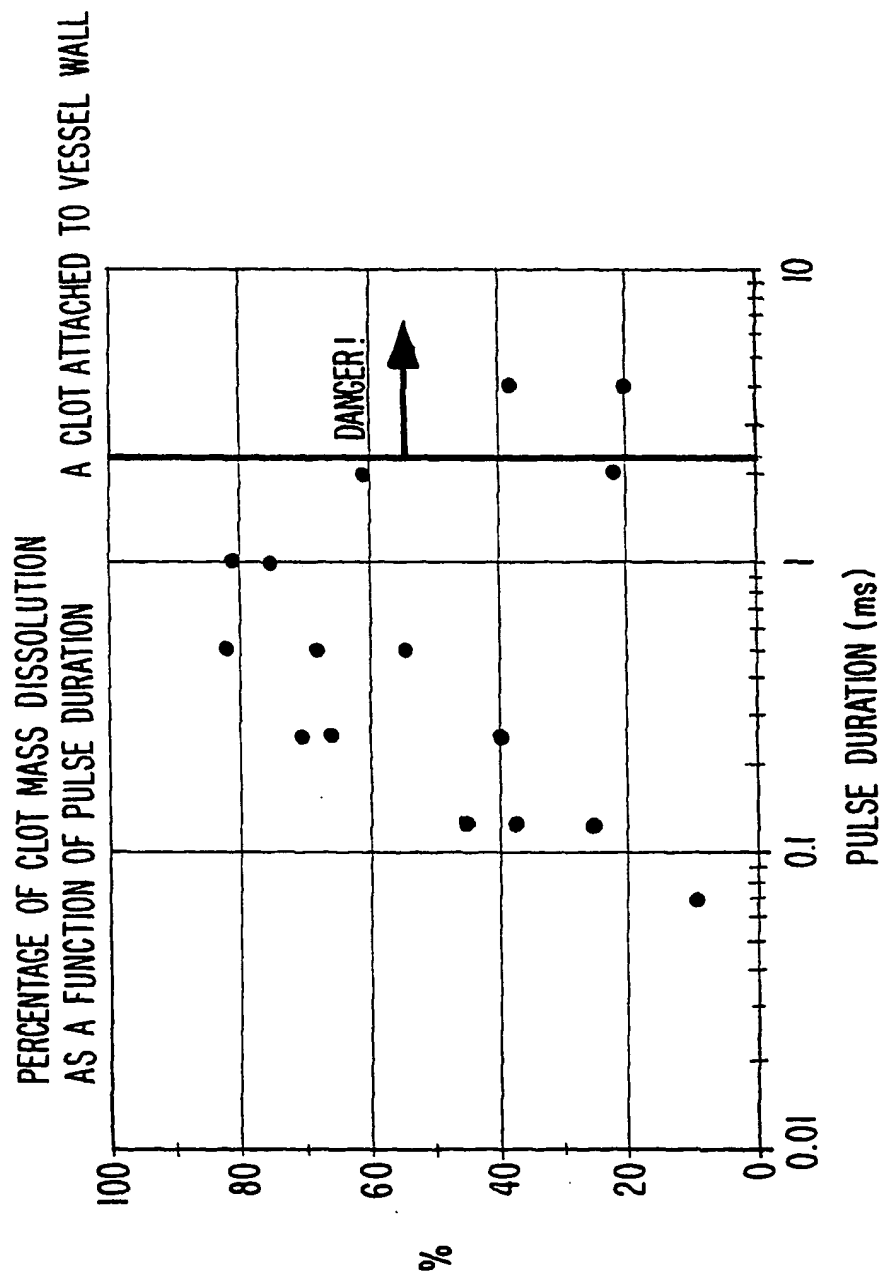
FIG. 7



DUTY CYCLE (T/T)=8
INTENSITY = 1300 W/cm²

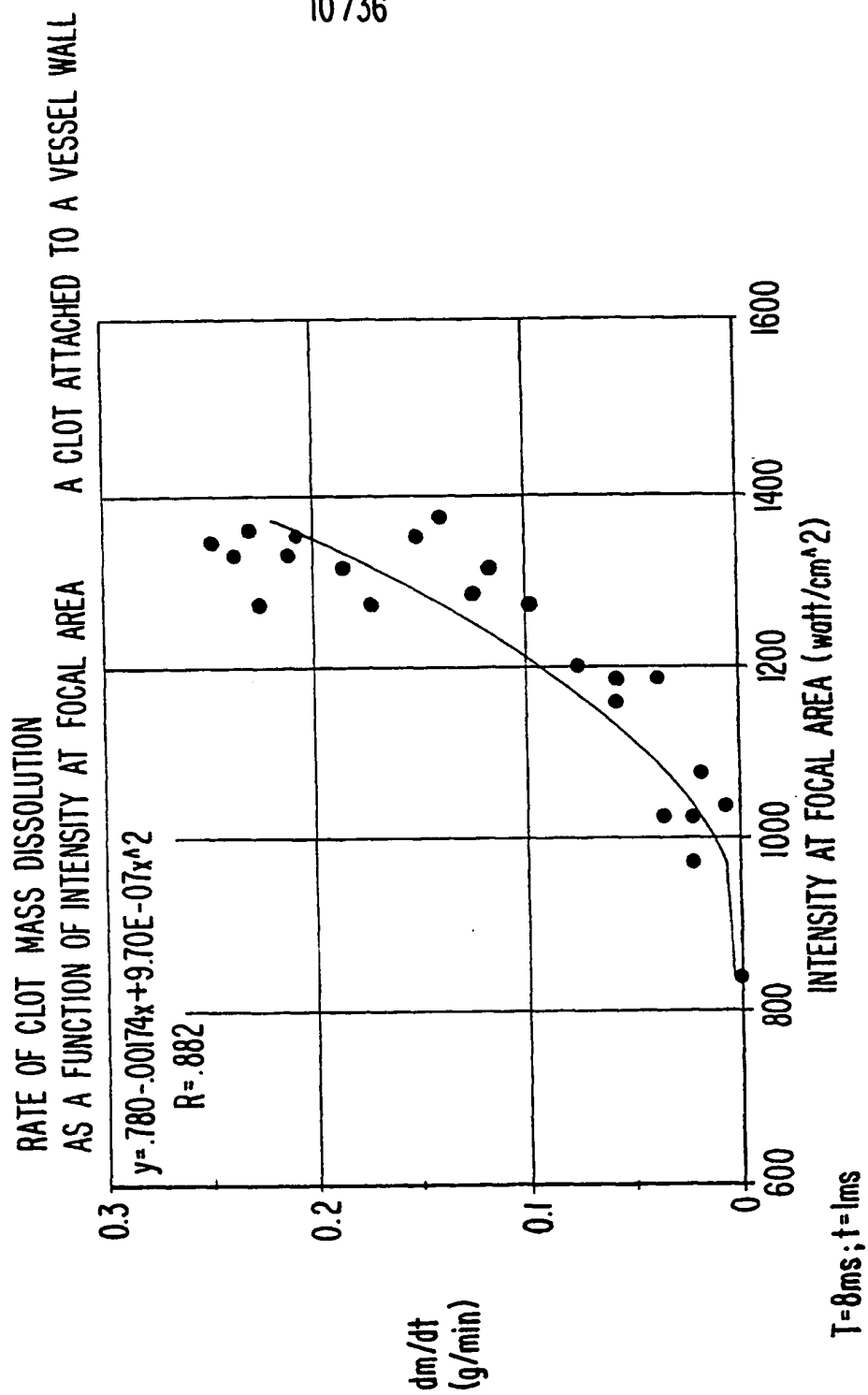
9/36

FIG. 8



$T = 8 \text{ ms}$
 $I = 1300 \text{ W/cm}^2$

FIG. 9



11/36

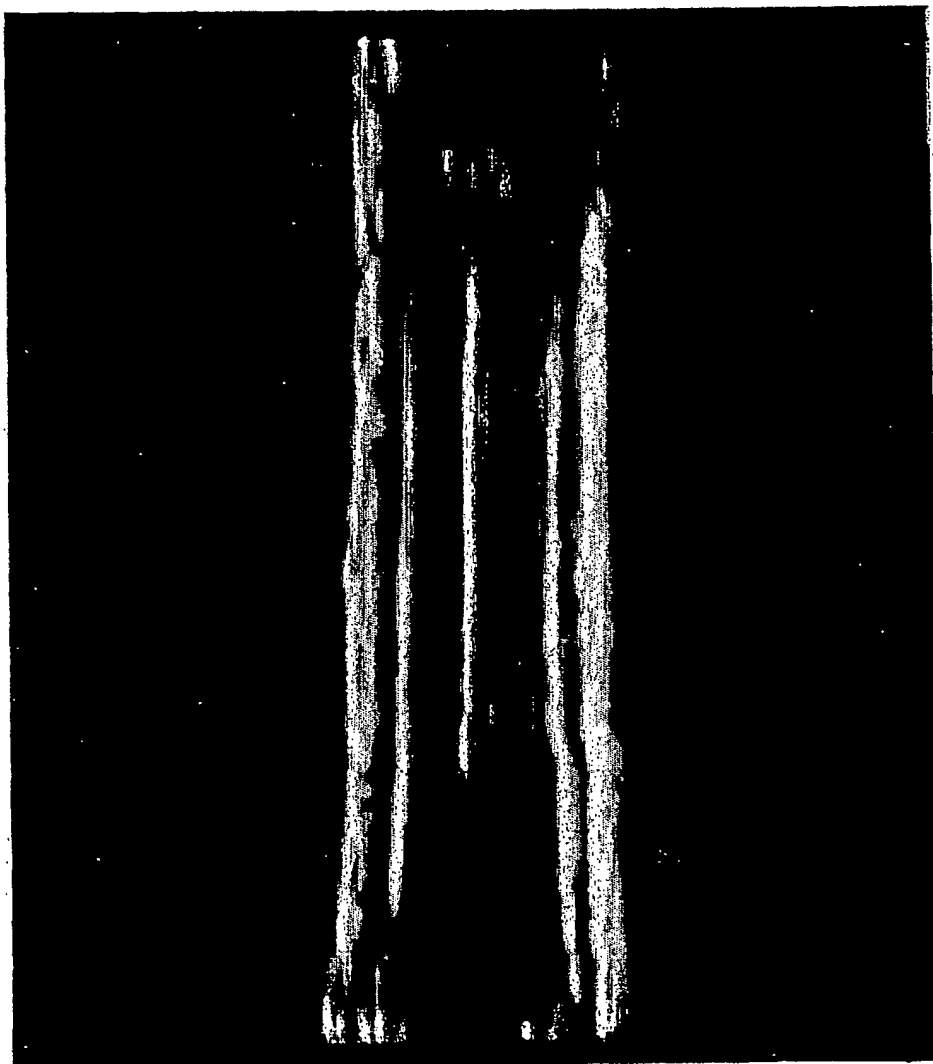


FIG. 10A

12/36

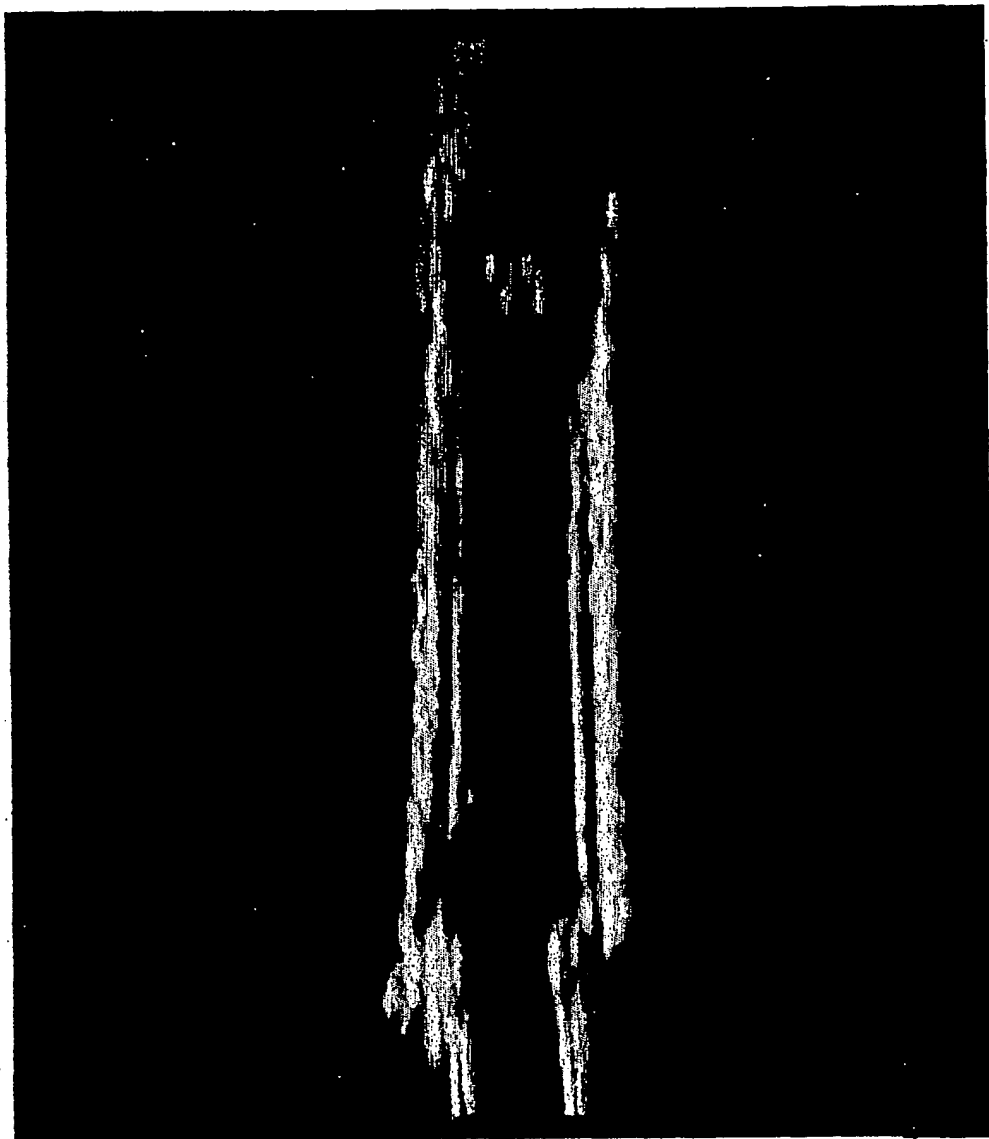
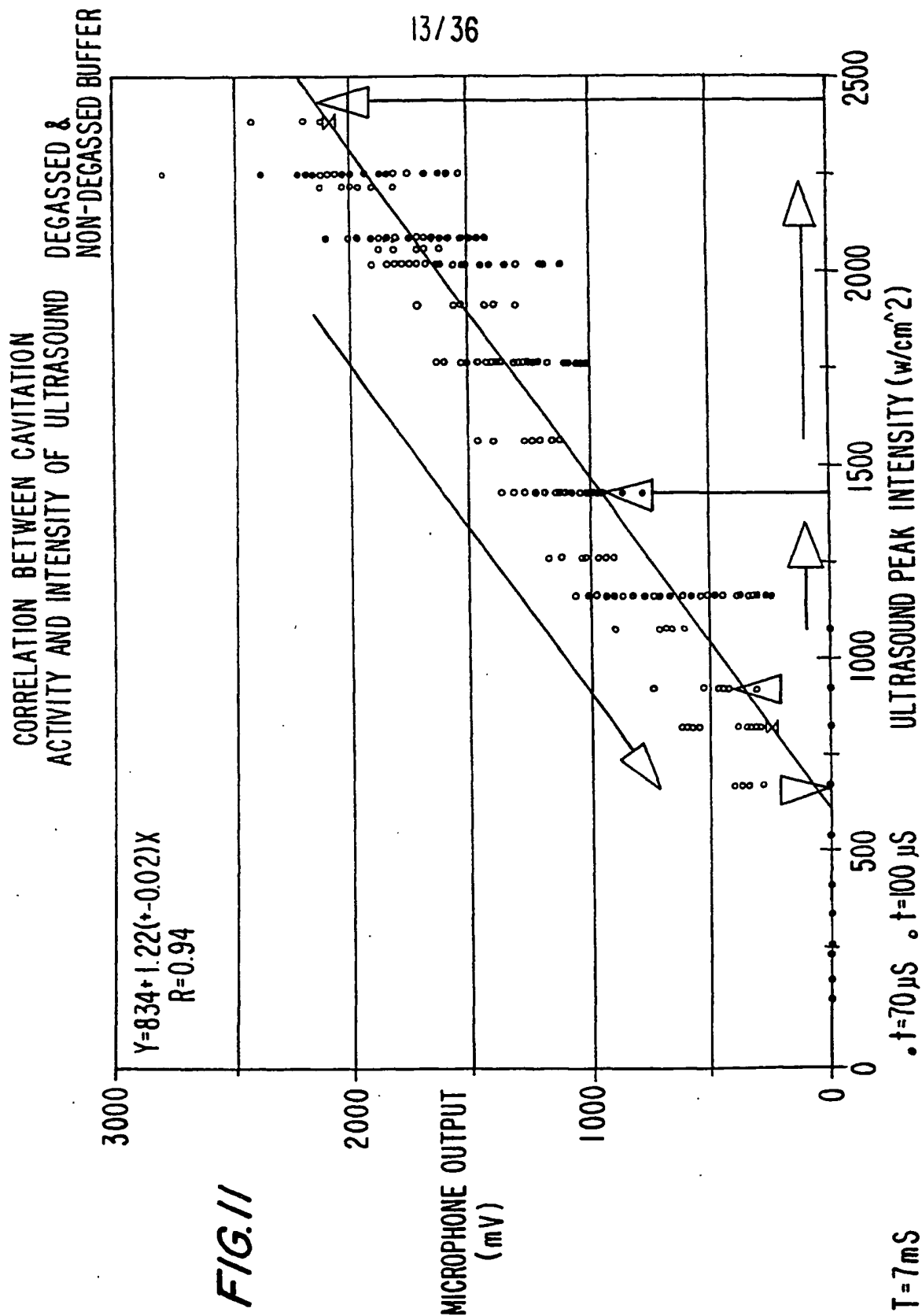
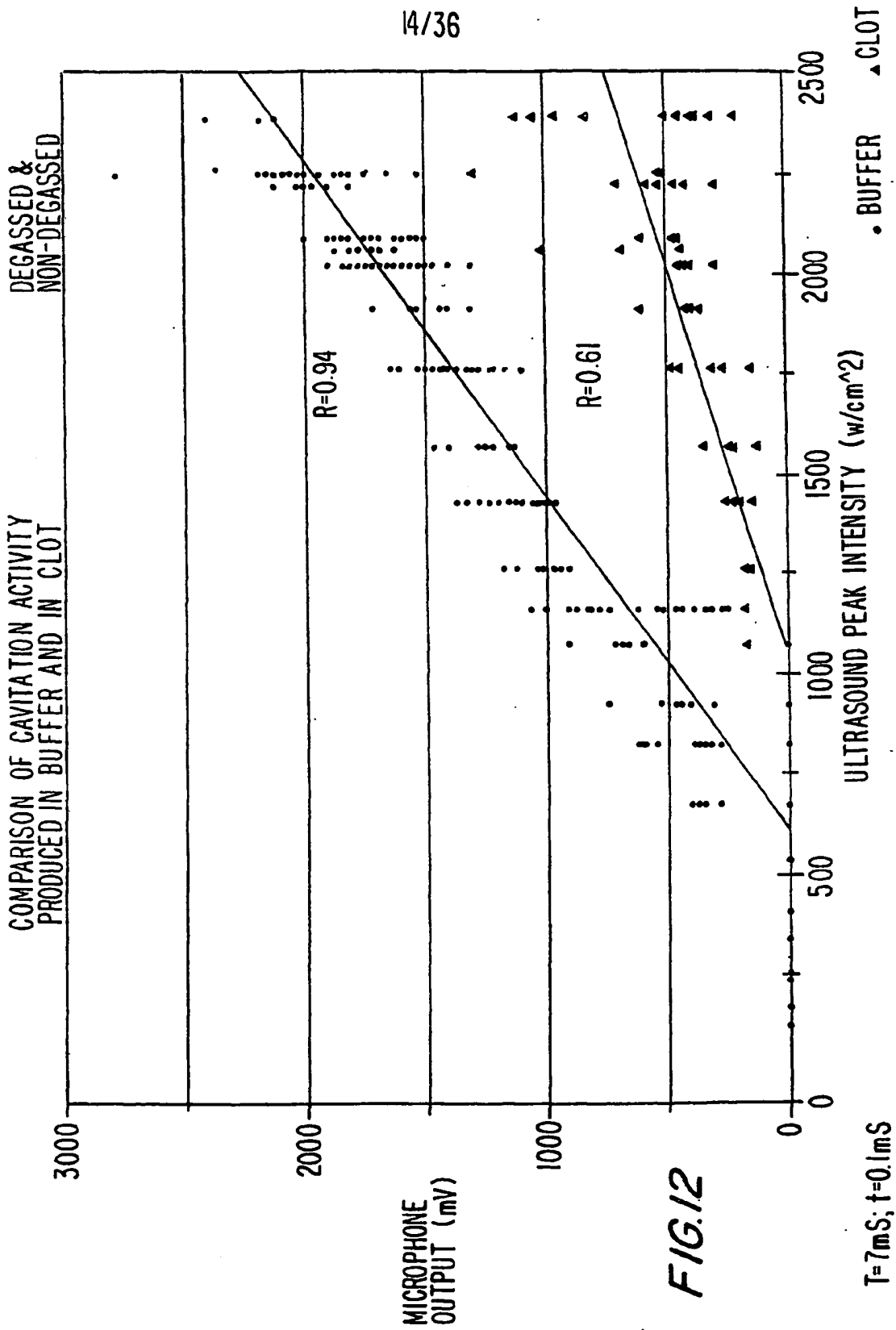


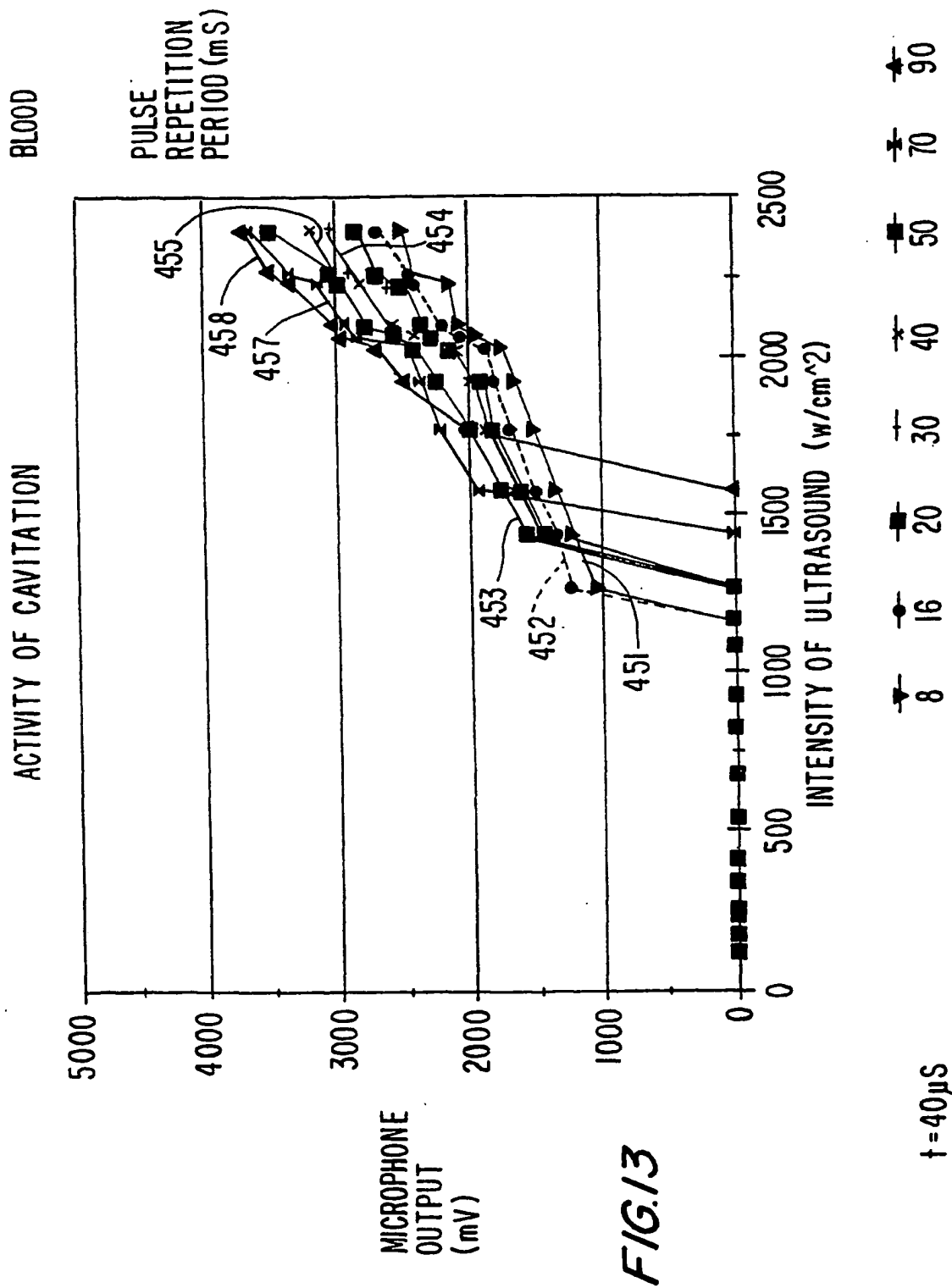
FIG. 10B



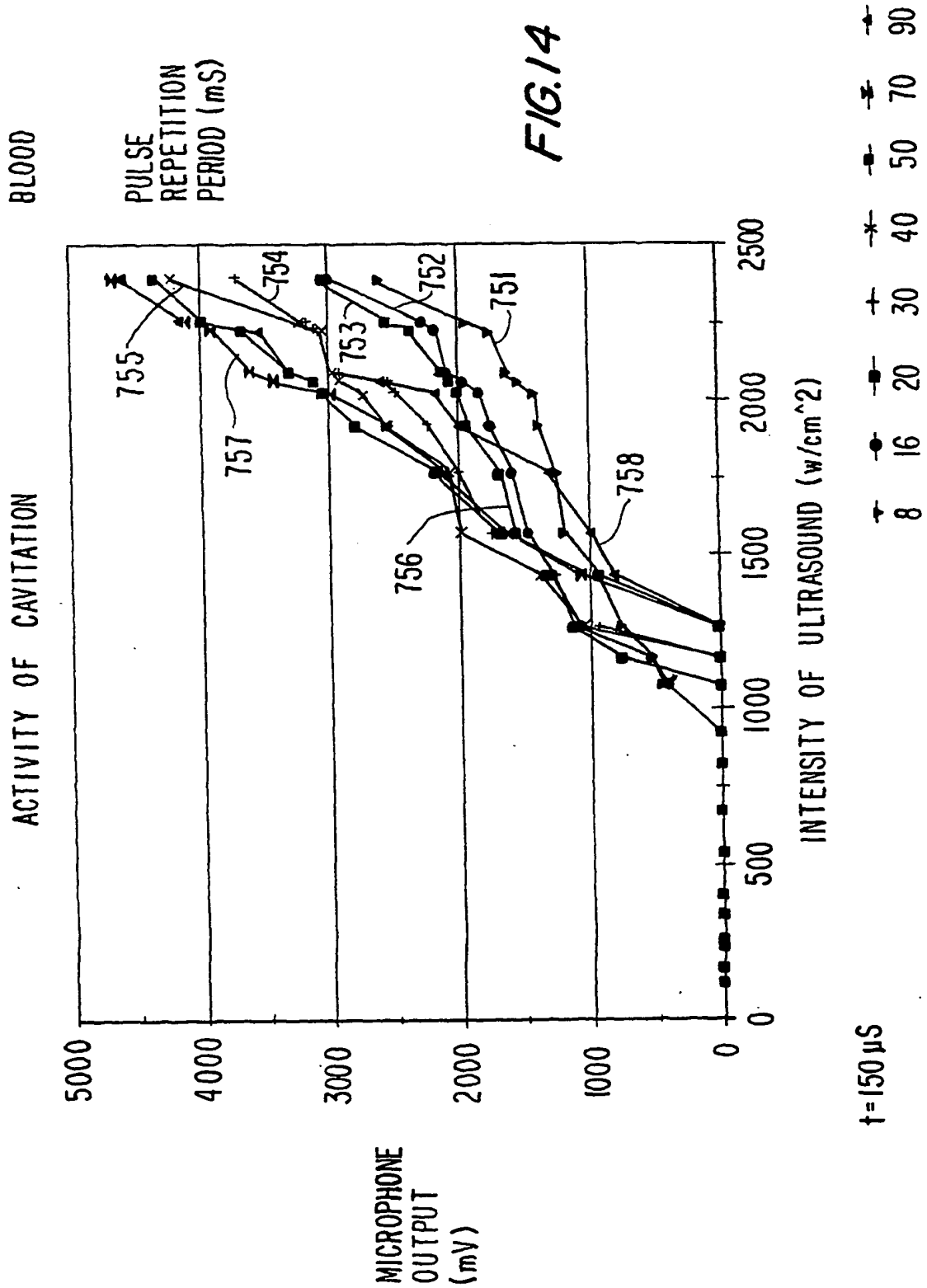
14/36



15/36



16/36



17/36

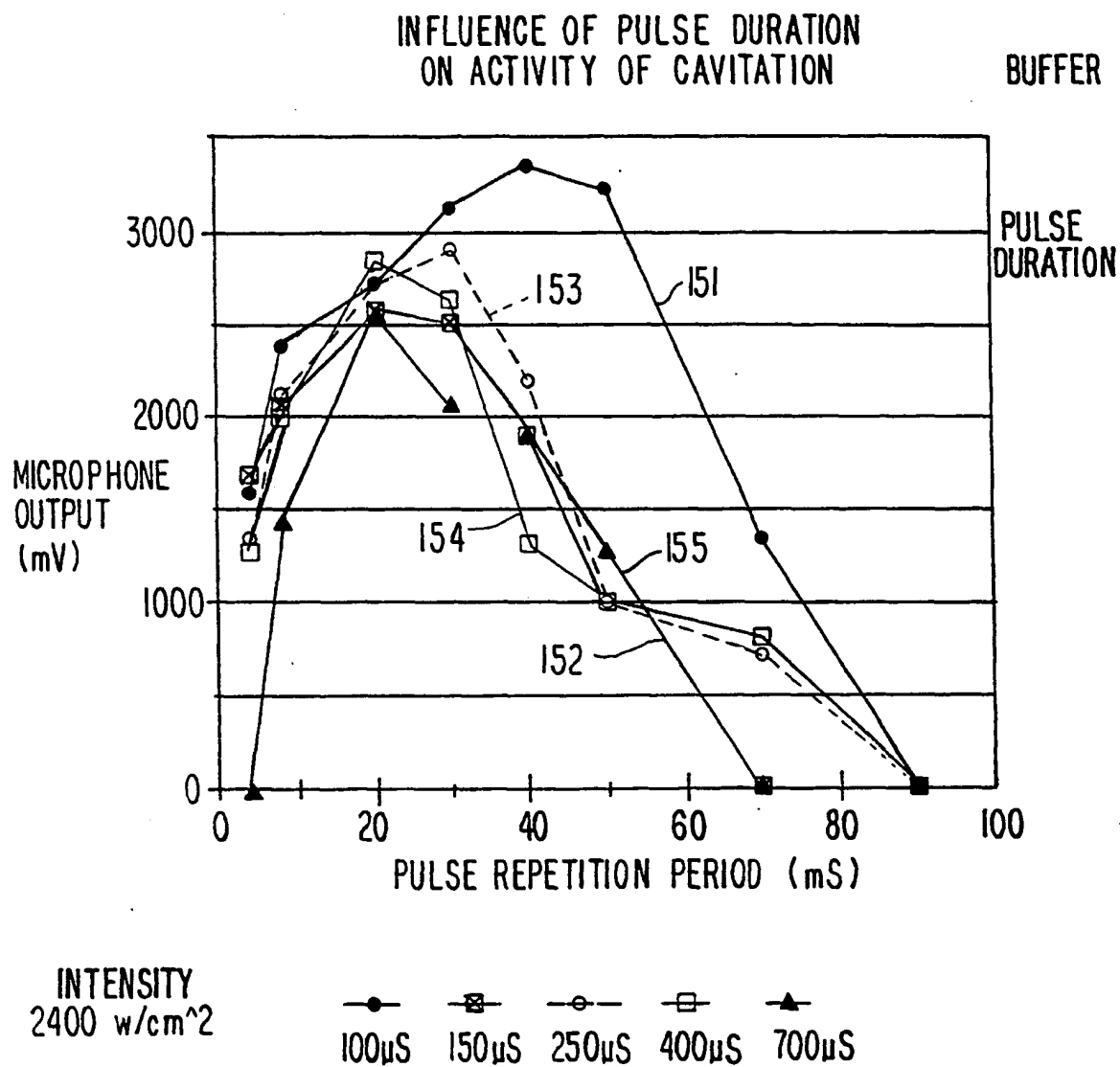
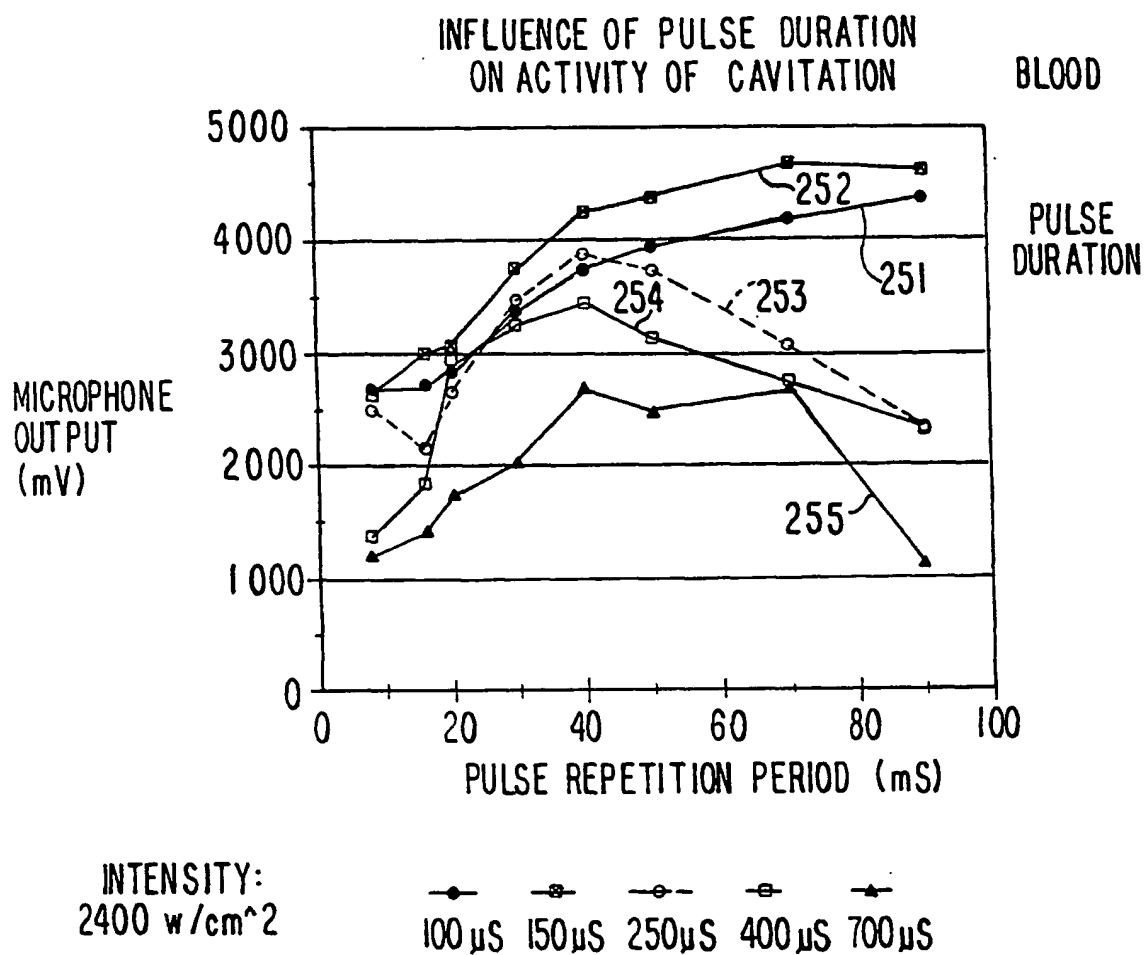


FIG. 15

18/36

**FIG. 16**

19/36

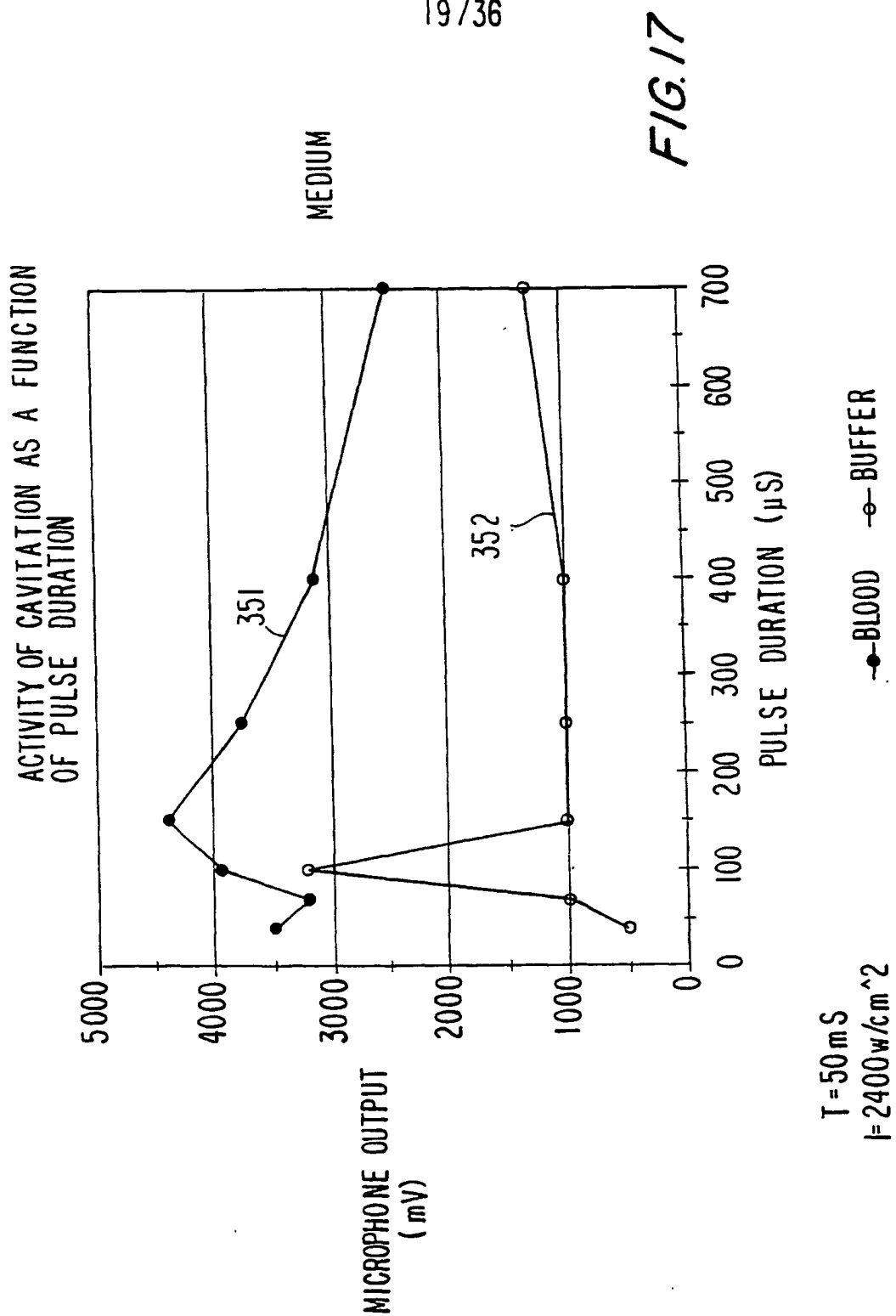
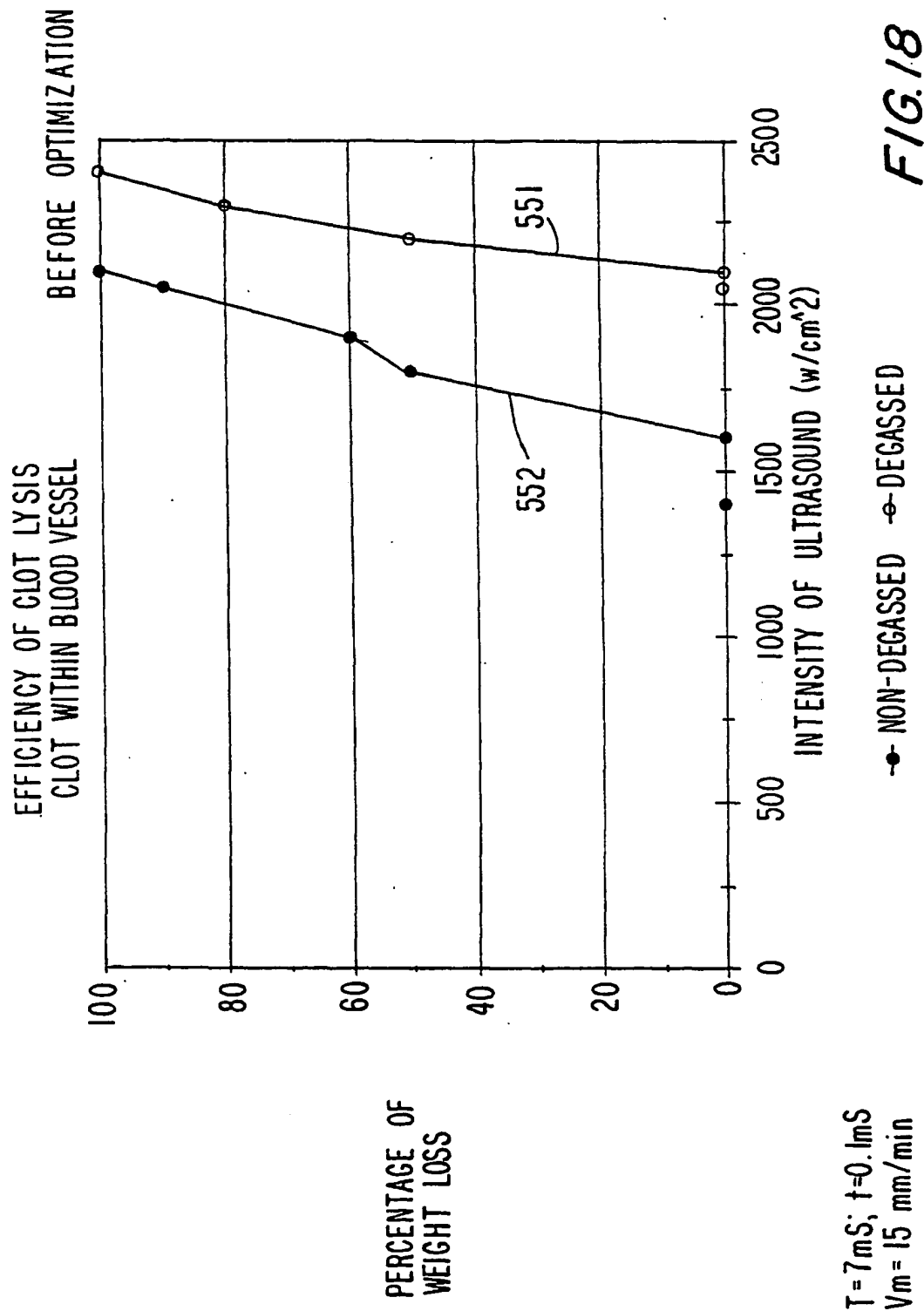


FIG. 17

20/36



21/36

SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

FIG. 19A

CLOT WITHIN BLOOD VESSEL

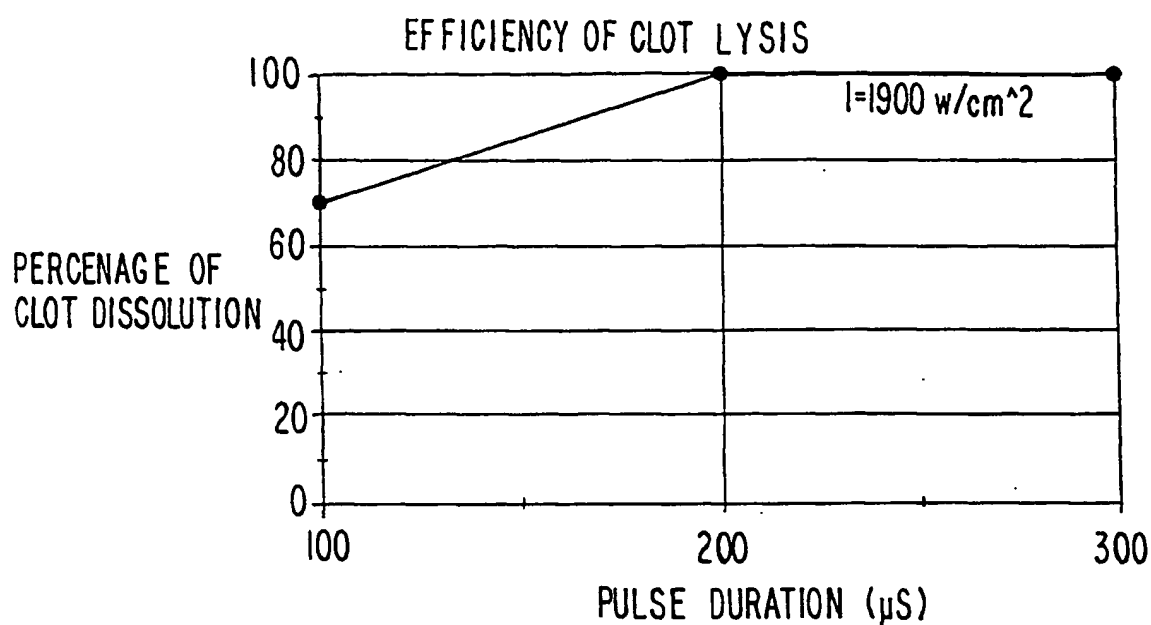
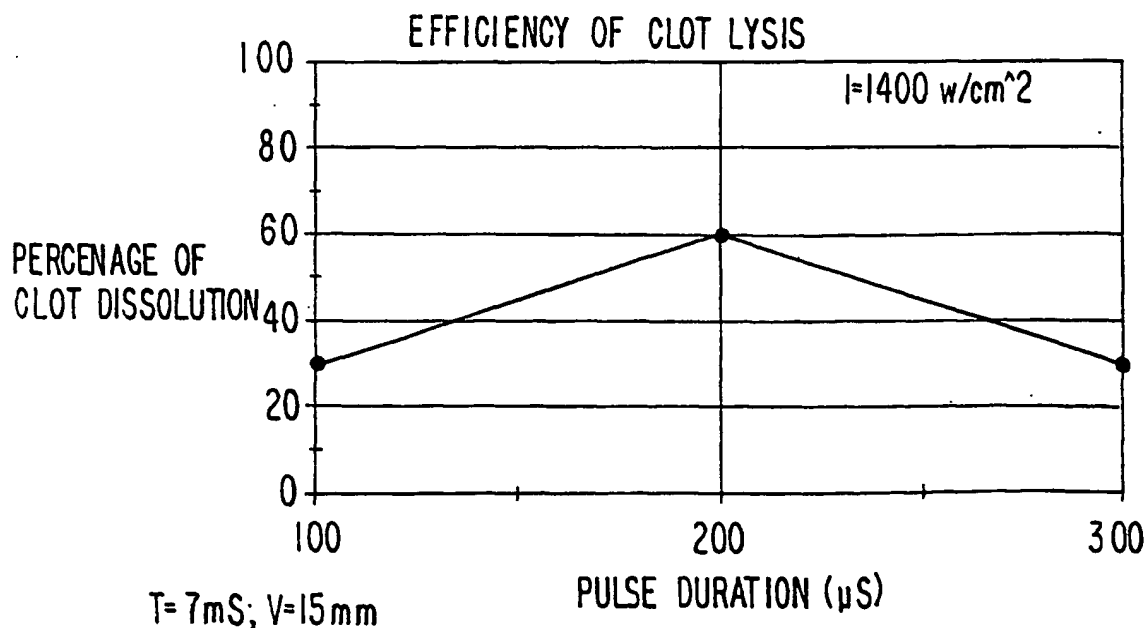
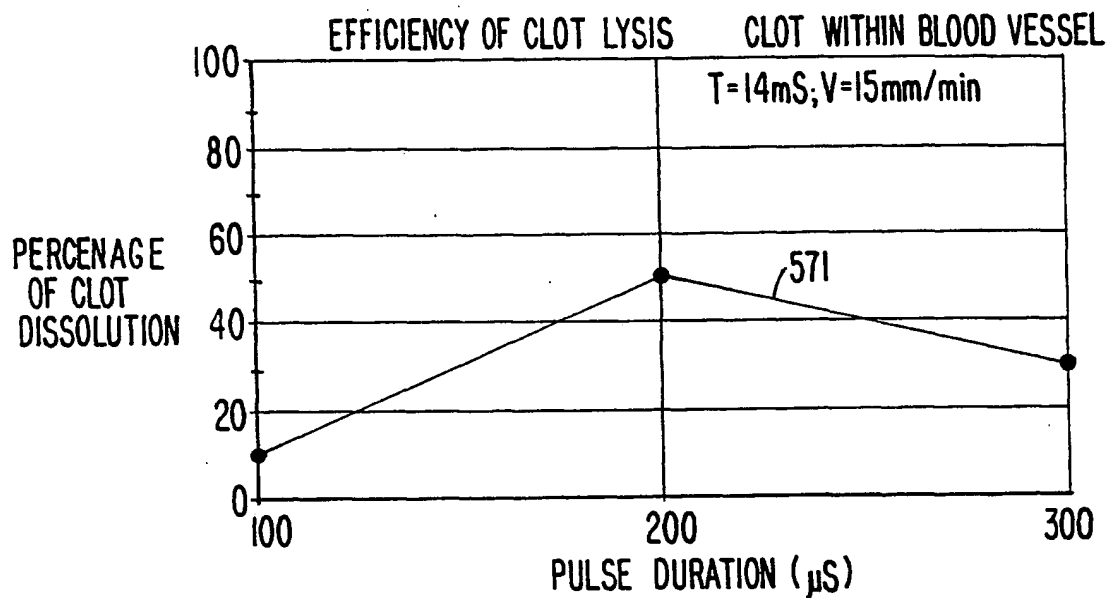
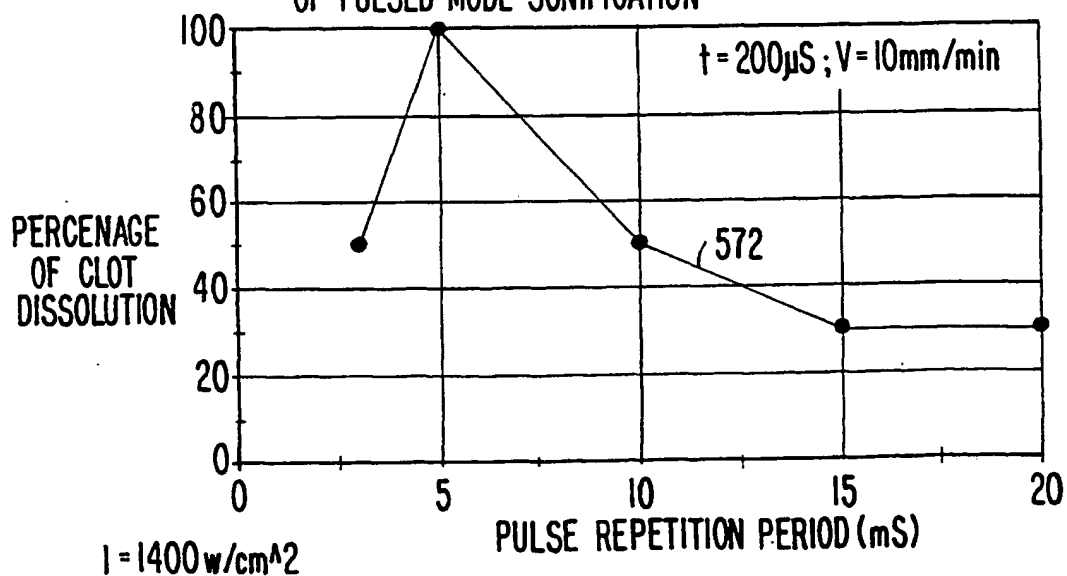
SEARCH FOR OPTIMUM TIME PARAMETER
OF PULSED MODE SONIFICATION

FIG. 19B

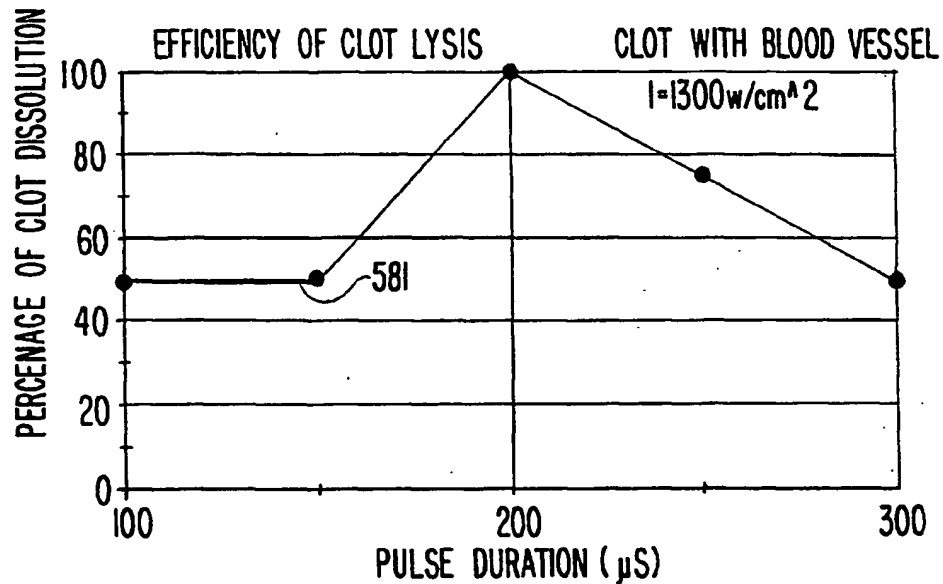
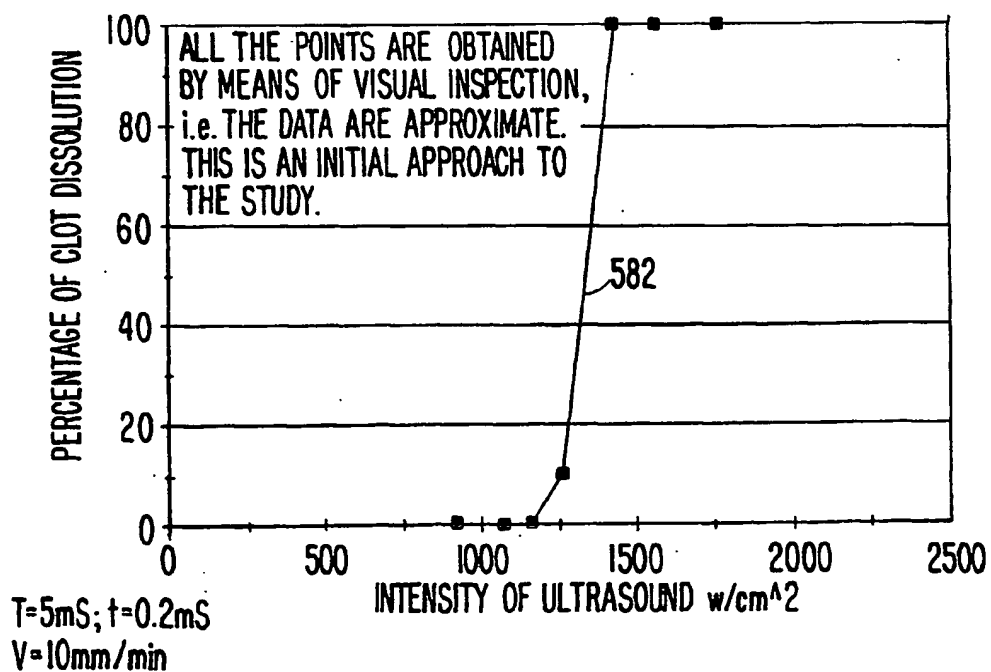
CLOT WITHIN BLOOD VESSEL



22/36

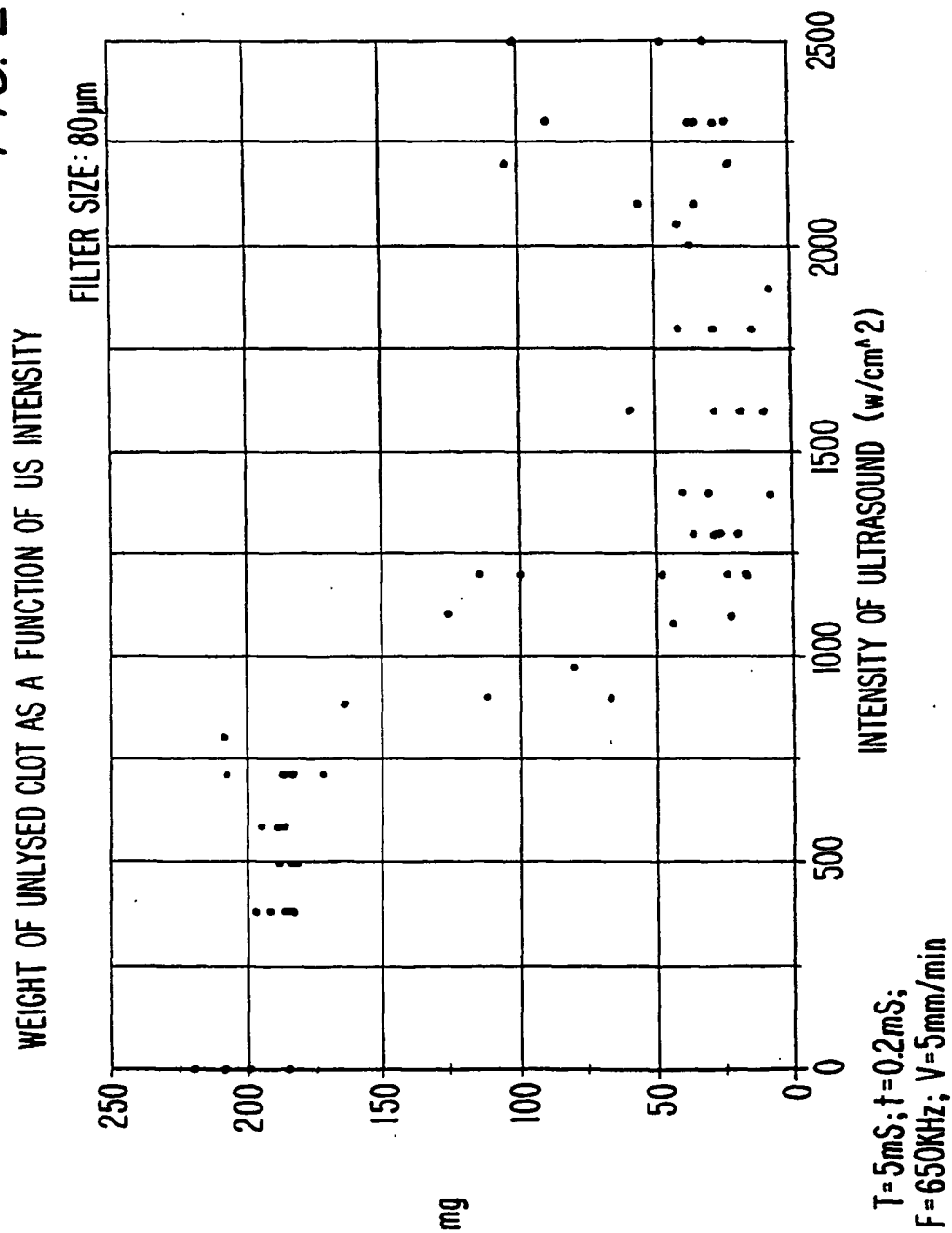
FIG. 20ASEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION**FIG. 20B**SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

23/36

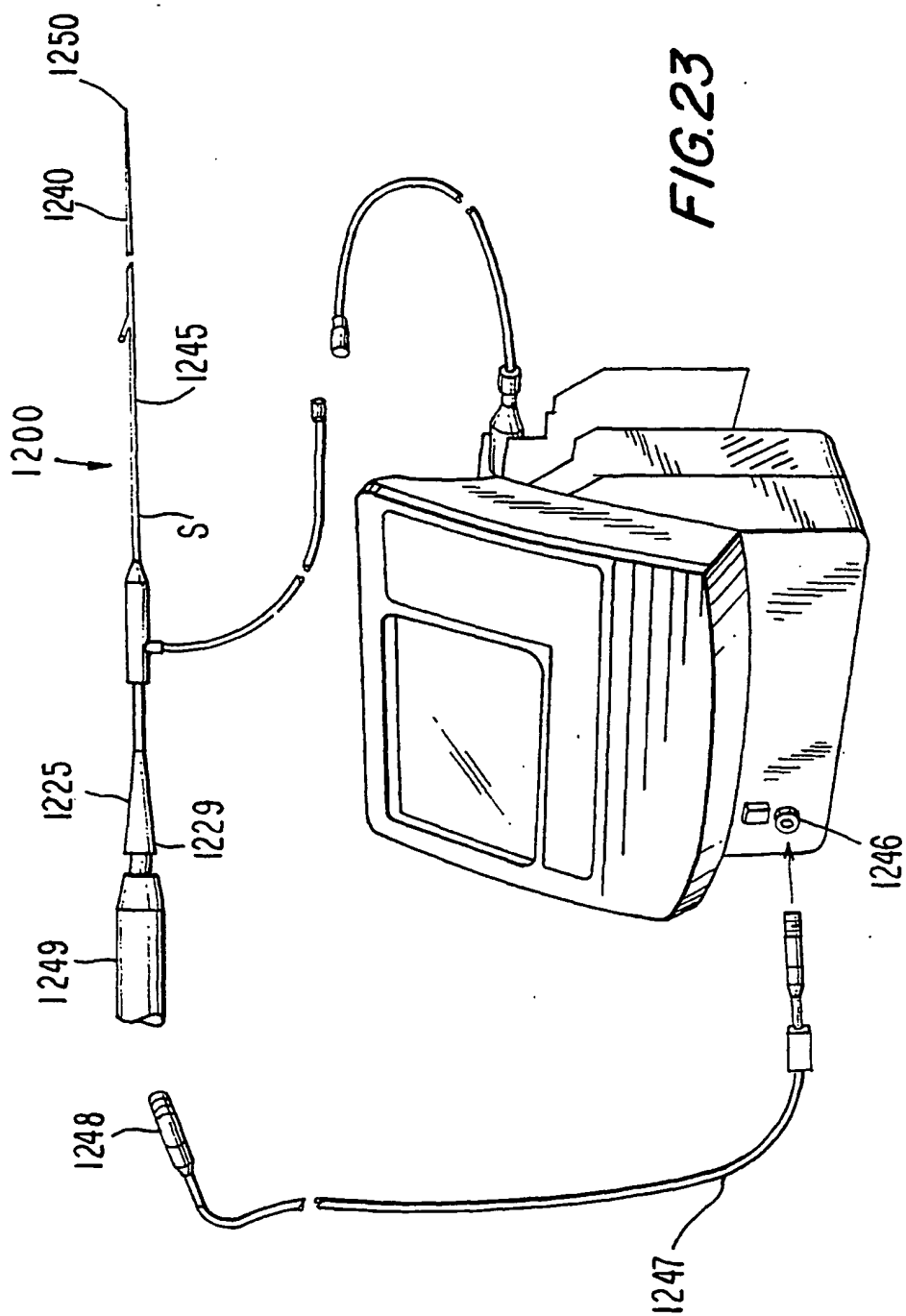
FIG.20CSEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION**FIG.21**SEARCH FOR OPTIMUM TIME PARAMETERS
OF PULSED MODE SONIFICATION

24/ 36

FIG. 22



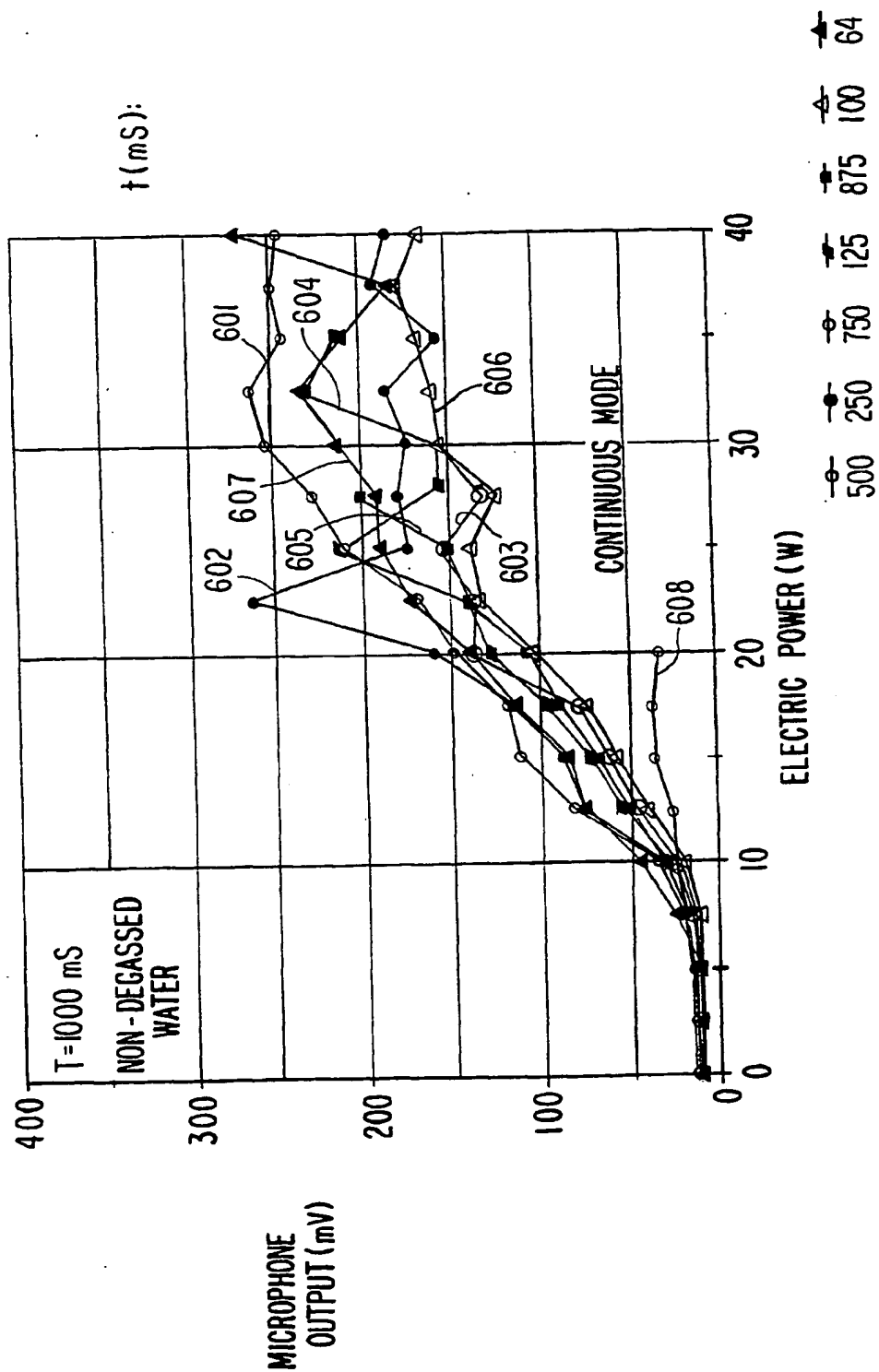
25/36



26/36

FIG. 24

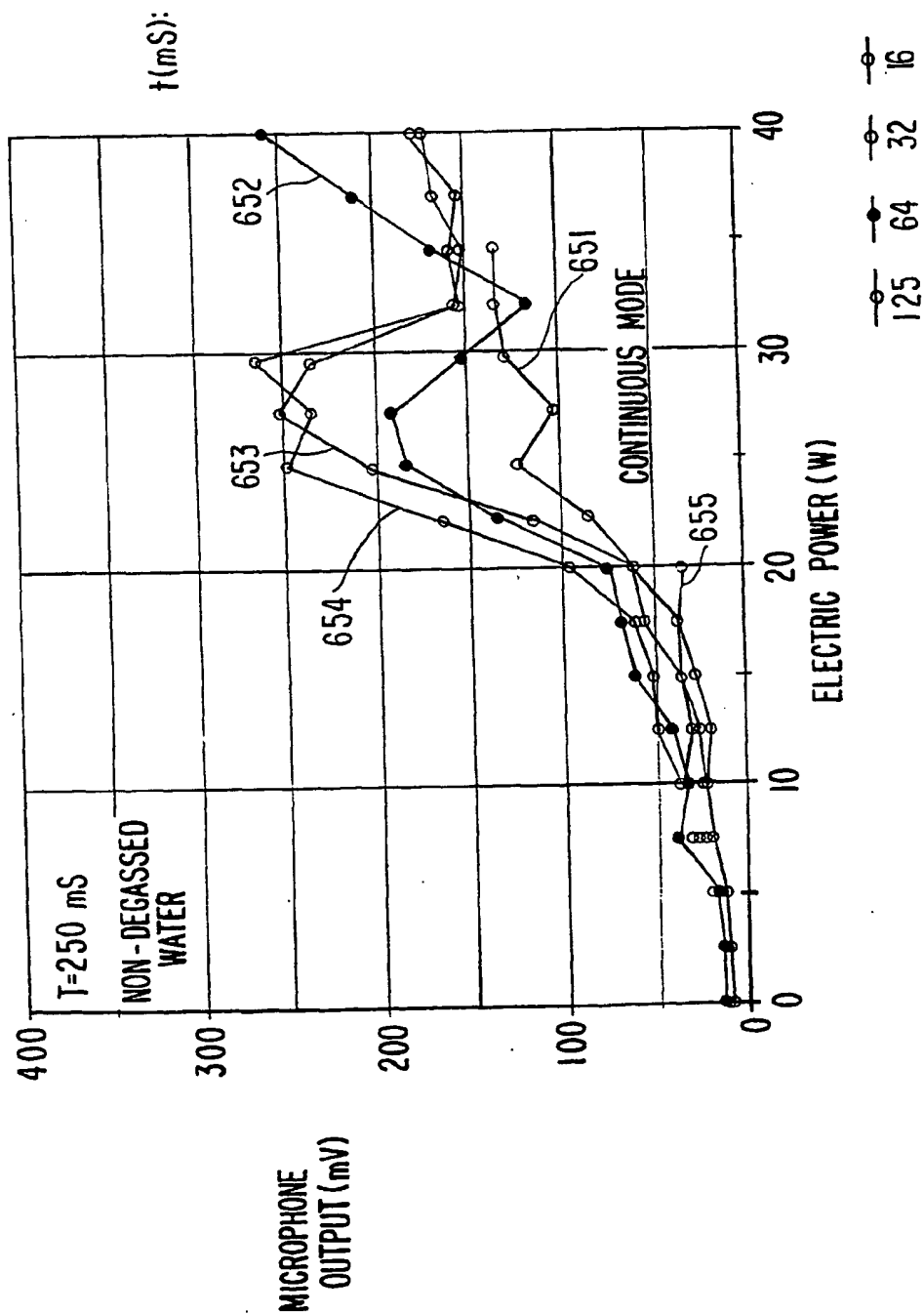
VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER

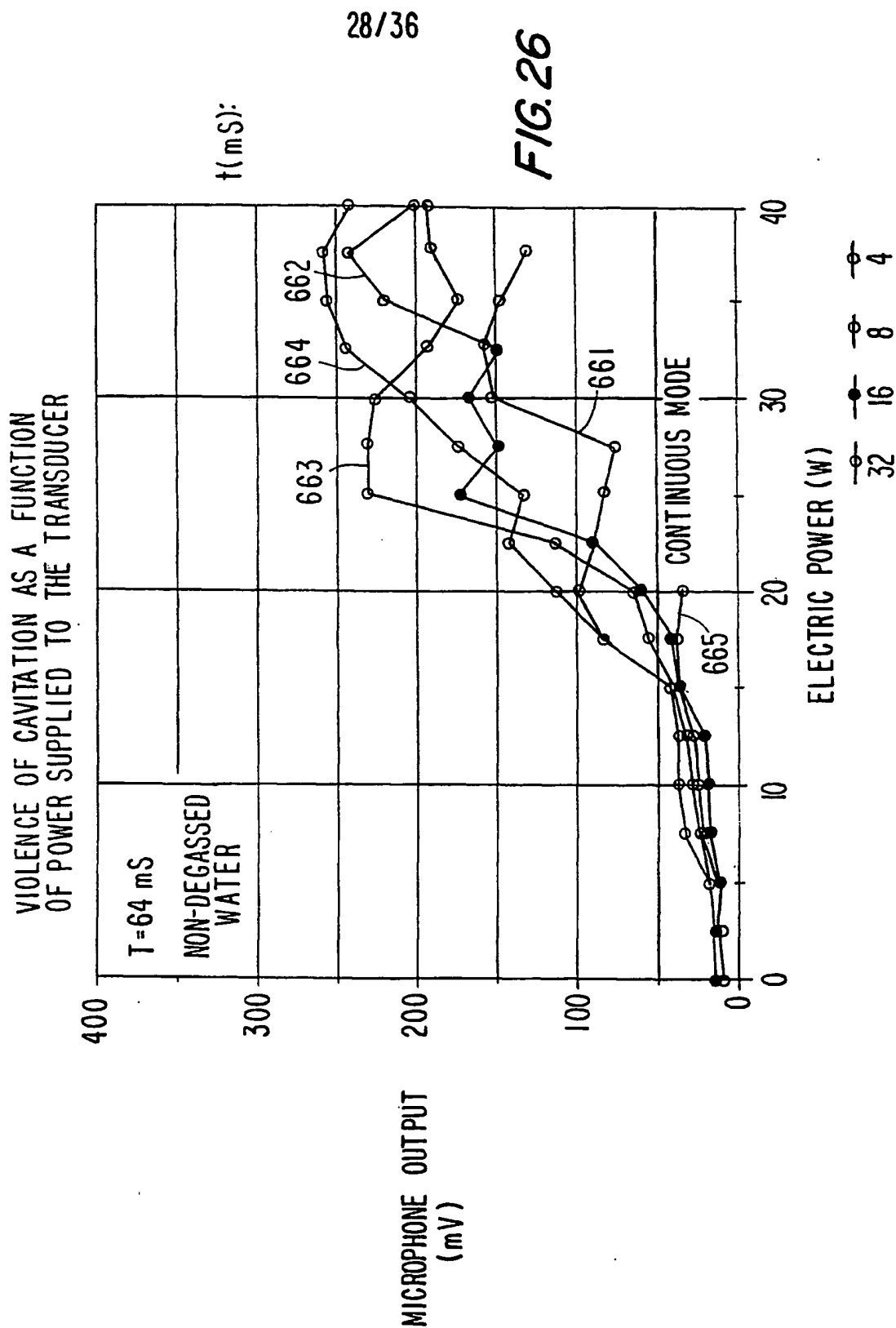


27/36

FIG. 25

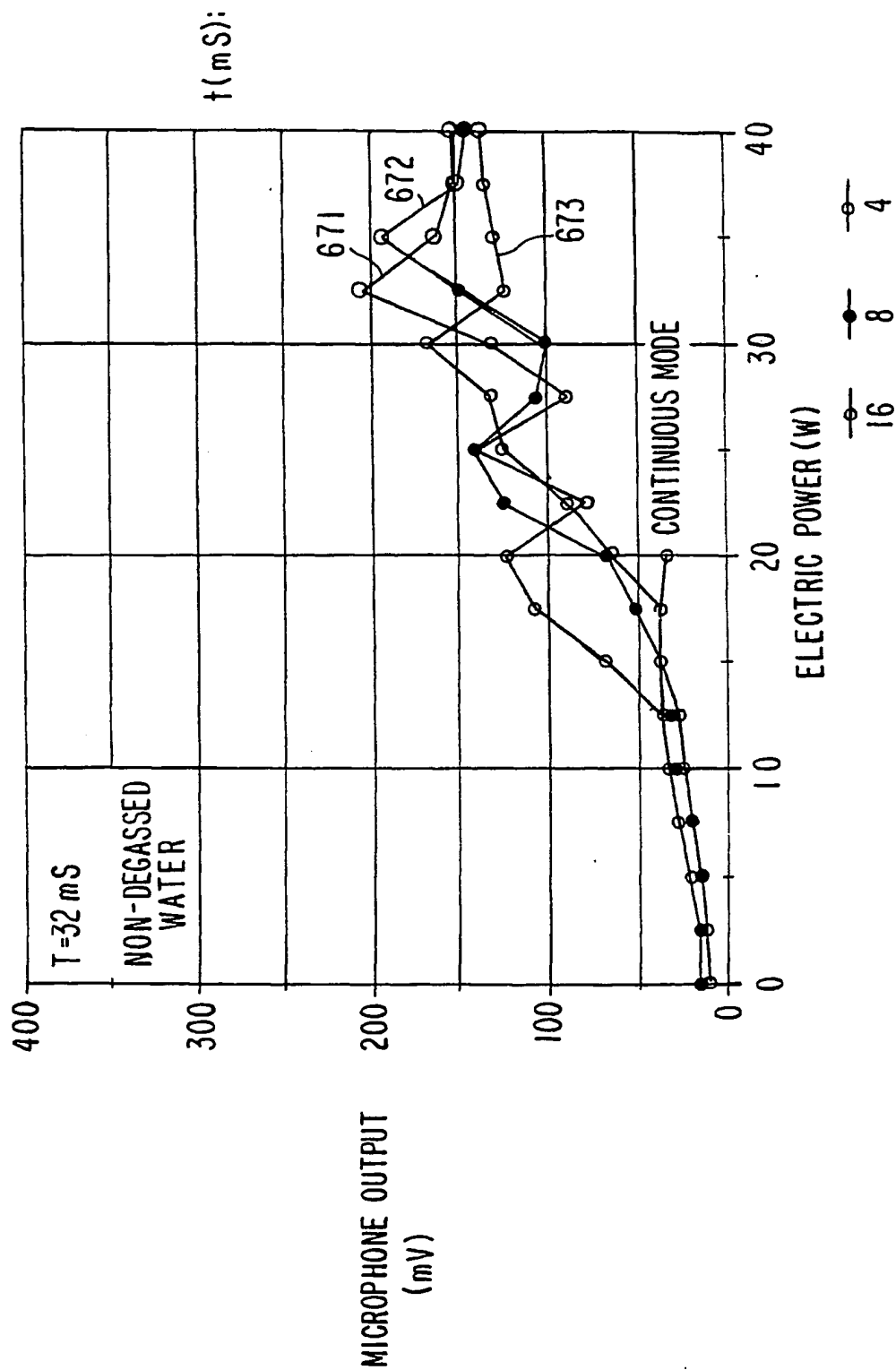
VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER





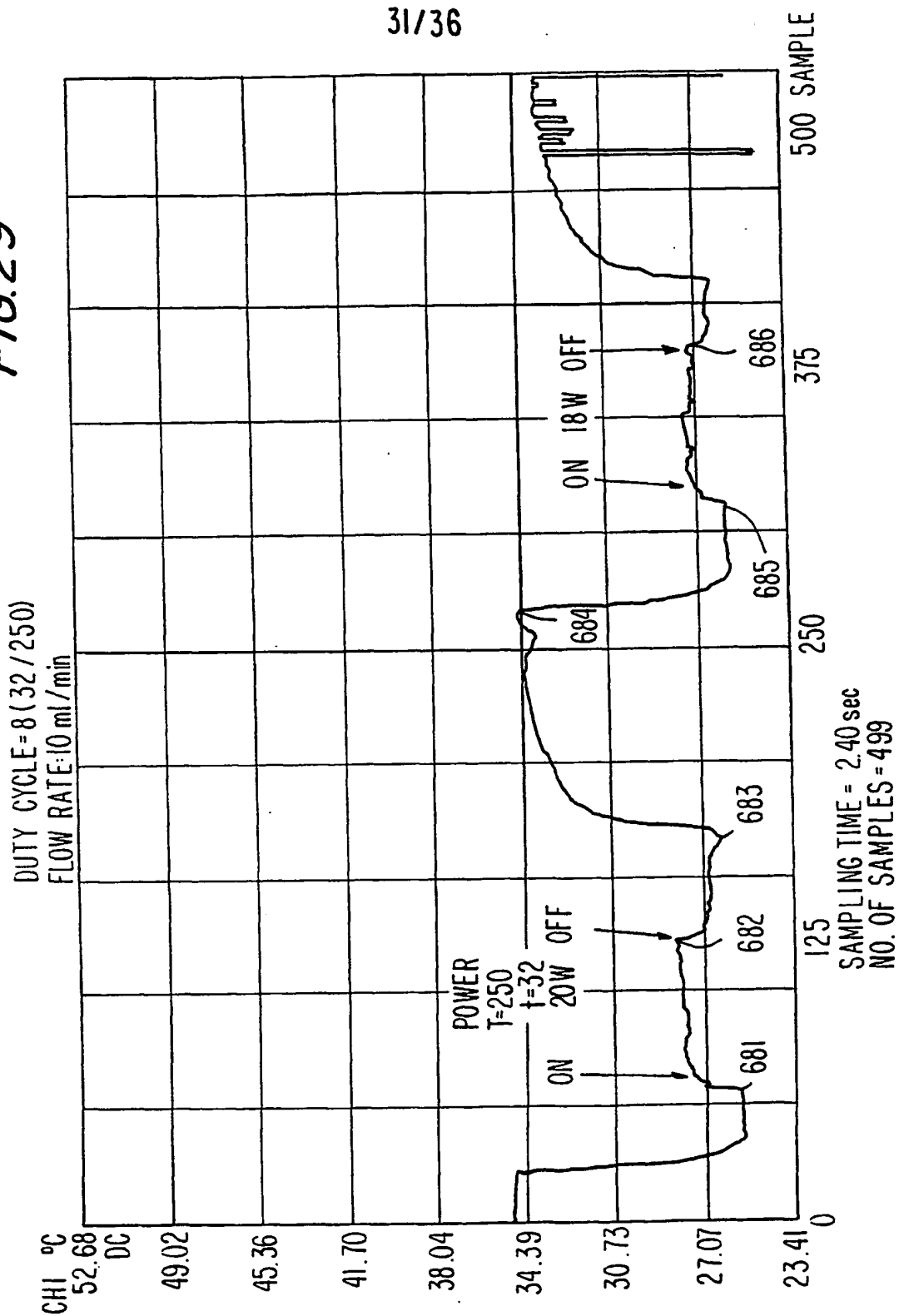
29/36

FIG. 27

VIOLENCE OF CAVITATION AS A FUNCTION
OF POWER SUPPLIED TO THE TRANSDUCER

31/36

FIG. 29



32/36

FIG. 30

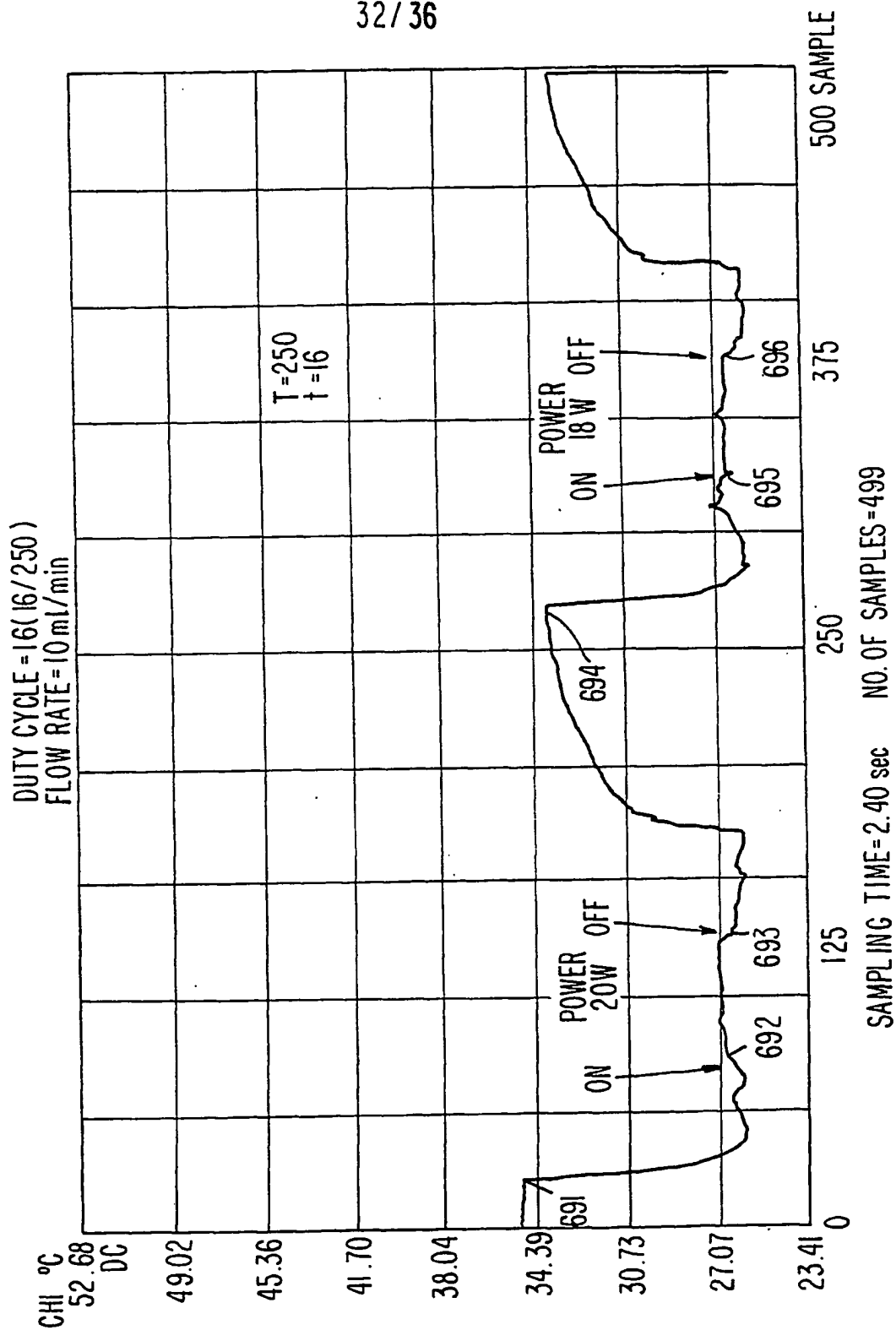
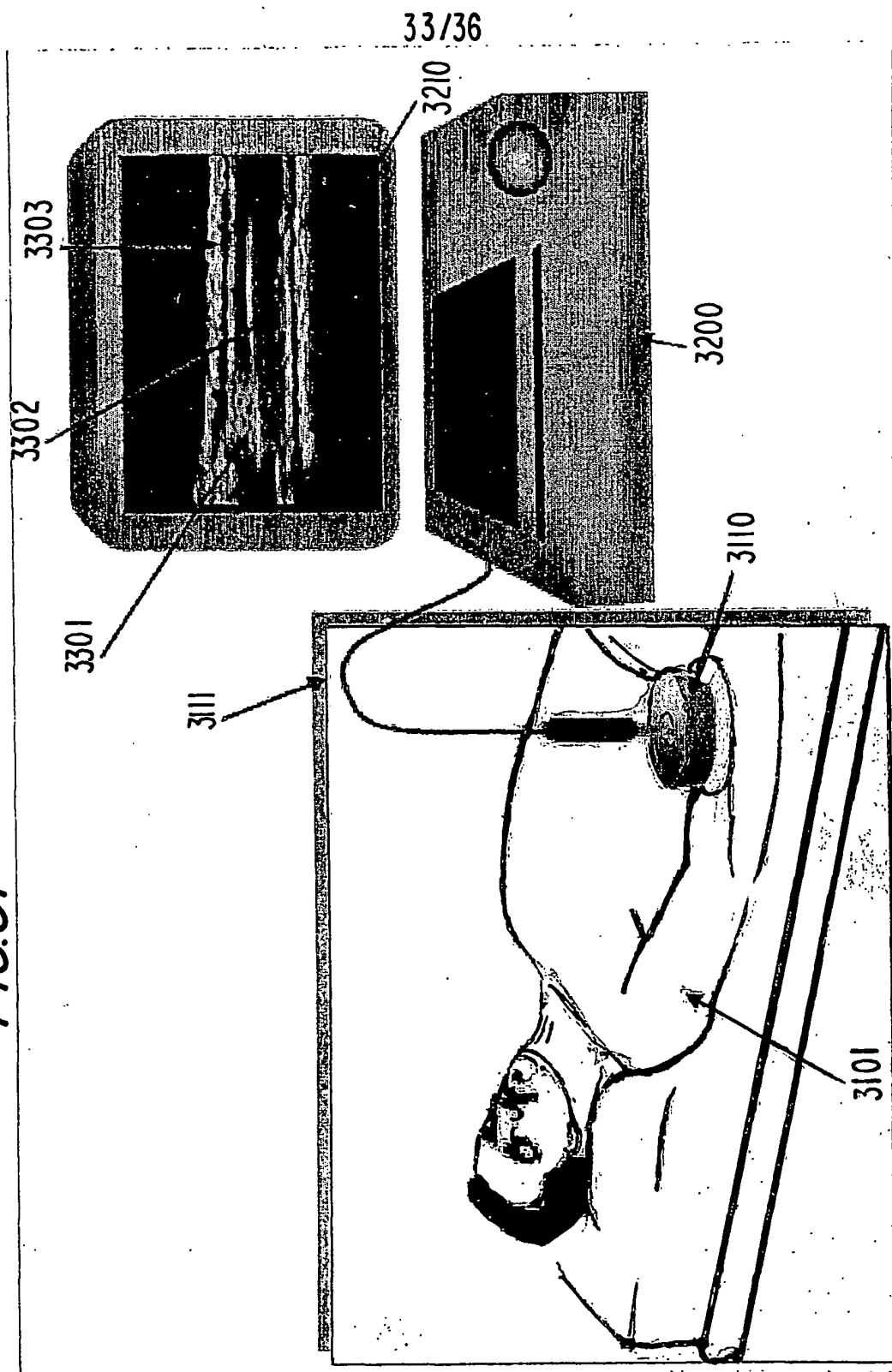


FIG. 31



34/36

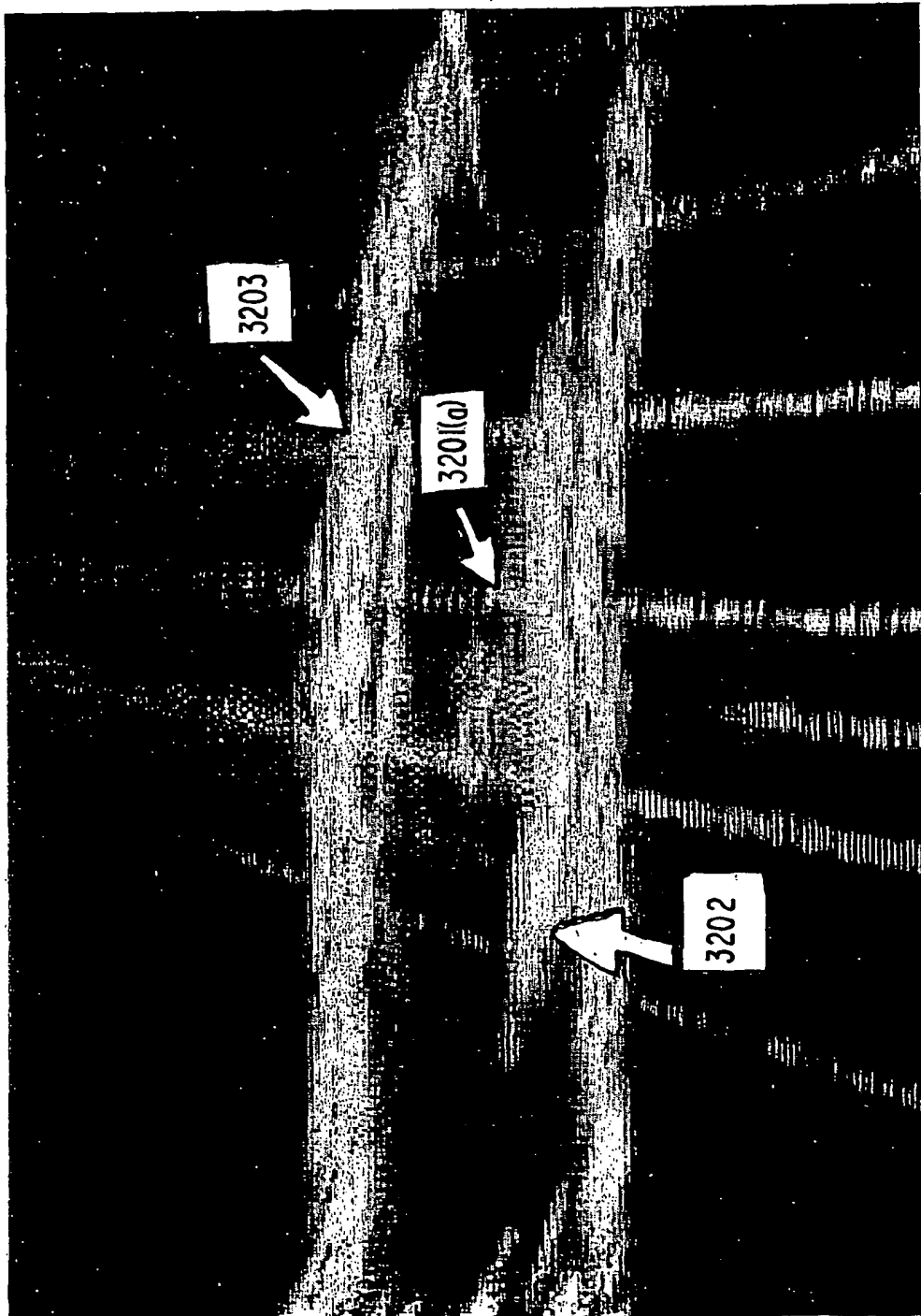
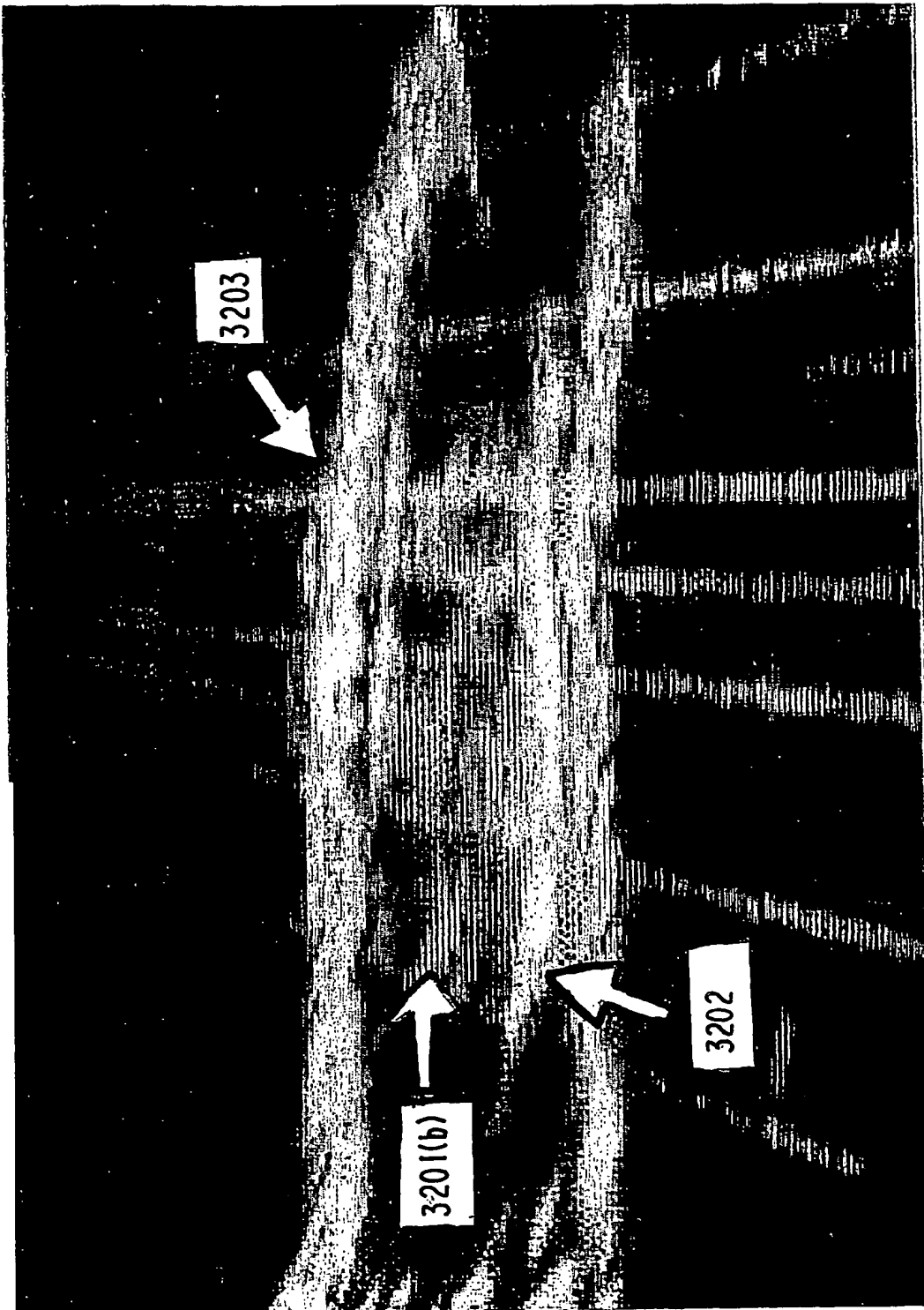


FIG. 32A

35/36

FIG. 32B



36/36

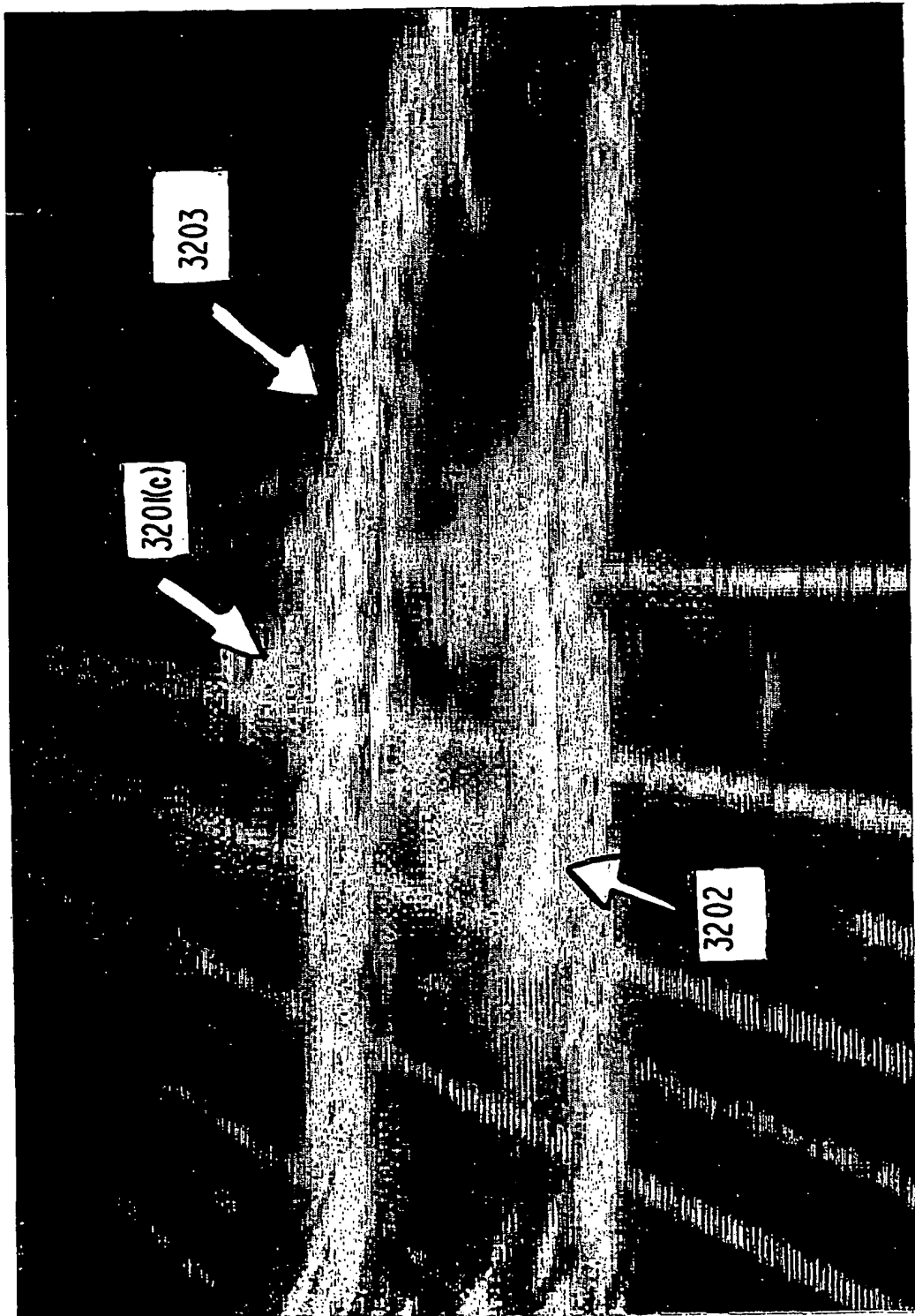


FIG. 32C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05982**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A61N 7/00

US CL :600/439; 601/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 601/2-4 ; 600/439

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,827,204 A (GRANDIA et al.) 27 October 1998, entire document.	1, 3, 5, 7, 8, 10, 13
A	US 5,582,578 A (ZHONG et al.) 10 December 1996, Abstract.	1, 3, 5, 7, 8, 10, 13
A	US 5,601,526 A (CHAPELON et al.) 11 February 1997, entire document.	1, 3, 5, 7, 8, 10, 13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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document member of the same patent family

Date of the actual completion of the international search

22 MAY 2000

Date of mailing of the international search report

13 JUN 2000

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